Investigations into sulfamide as a phosphate isostere in anti-TB drug development

A thesis submitted in partial fulfilment of the requirements for the degree of **Doctor of Philosophy** in **Chemistry** at the **University of Canterbury**

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Abstract

Two major oligosaccharides, lipoarabinomannan (LAM) and arabinogalactan (AG), are important constituents of the cell wall of *Mycobacterium tuberculosis*, the causative bacterial pathogen of tuberculosis. The AG, which is attached to long chain lipids, provides a very effective hydrophobic barrier against the penetration of anti-mycobacterial drugs. The LAM and AG consist of varying numbers of arabinofuranose residues. The biosynthesis of the arabinan portion of both is postulated to involve multiple arabinofuranosyltransferases (AraT's), which catalyse the step-wise coupling of the donor decaprenolphosphoarabinose (DPA) to growing oligosaccharides. We have synthesized a series of *arabino* glycosyl sulfamides as potential inhibitors of mycobacterial cell wall biosynthesis. In this work sulfamide was used as an isostere of phosphate and varied the hydrophobic substituents as mimics of the polyprenol chain of DPA. However, arabino *N*-glycosyl sulfamides, sulfonamides, and sulfamates unexpectedly and spontaneously converted from the furanose to the pyranose form in an aqueous solution. To remedy this, a series of glycosyl sulfamides which lacked the 5-hydroxyl group were synthesized in order to fix these materials in the furanose form. All compounds were synthesised and tested for anti-mycobacterial activity using the Alamar Blue (AB) assay. Compounds displayed low to moderate activity against *M. smegmatis.*

The recently discovered enzyme *Mycobacterium tuberculosis* thymidine monophosphate kinase (TMPK*mt*), catalyses the phosphorylation of thymidine monophosphate (dTMP) to give thymidine diphosphate (dTDP), and is indispensable for the growth and survival of *M. tuberculosis*, as it plays an essential role in the DNA synthesis. Therefore, inhibition of TMPK*mt* may be an attractive avenue for the

development of novel anti-tuberculosis agents. Possible sulfamide structures were screened using *in silic*o induced-fit docking methods as dTMP analogues with TMPK*mt* X-ray crystal structure (PDB accession code: 1N5K). From these docking results, a selection of compounds was synthesized and the evaluated for any anti-mycobacterial activity. However, none of the compounds showed promising inhibitory activity against *M. smegmatis.*

A novel reduction method was accidentally discovered during the synthesis of 6-amino-D-mannose pyranose, using iodide and Amberlite IR 120 ion exchange resin (H^+ form). During this process, D-mannose was first selectively iodinated using an Appel reaction, subsequent nucleophilic substitution using NaN_3. Following that reaction, in order to remove the imidazole, the reaction mixture was filtered through Amberlite IR 120 ion exchange resin (H^+ form), and then concentrated *in vacuo*. Interestingly, the final product was identified as the amine. As it is simple, efficient, and mild reduction method for the conversion of azides into amines, the reaction condition was optimized using NaI/Amberlite IR120 (H^+ form), and tolerance of the functional groups also investigated.

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Abbreviations

The following abbreviations have been used in this thesis:
General:

δ	chemical shift
ν_{max}	wavenumber
^{o}C	degrees Celsius
µm	micrometer
µM	micromolar
AB assay	alamar blue assay
Å	Angstrom
Ac	acetyl
AcCl	acetylchloride
AG	arabinogalactan
anti-TB	anti-tuberculosis
aq	aqueous
Ara*f*	arabinofuranose
AraT's	arabinofuranosyltransferases
Ar	aromatic
at	apparent triplet (in NMR)
ATP	adenosine triphosphate
AZT-MP	3'-azido-3'-deoxythymidine monophosphate
$BF_3.Et_2O$	boron trifluoride diethyl etherate
Bn	benzyl
br.	broad (in NMR)
Bz	benzoyl
c	concentration
Calcd.	calculated
CEC	cation exchange chromatography
cm	centimeter
COSY	correlation spectroscopy
d	doublet (in NMR)
D_2O	deuterated water

DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
dCTP	deoxycytidine triphosphate
dTMP	deoxythymidine monophosphate
dUTPase	deoxyuridine triphosphatase
dTDP	deoxythymidine diphosphate
dd	doublet of doublets (in NMR)
DEPT	distortionless enhancement by polarization transfer
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
e.g.	*exempli gratia* (for example)
DPA	decaprenyl phosphoarabinose
DPPR	decaprenylphosphoryl-5-phosphoribose
DPR	decaprenylphosphorylribose
DS-TB	drug-susceptible tuberculosis
DTBMP	di-*tert*-butylmethylpyridine
dTTP	deoxythymidine triphosphate
EMB	ethambutol
ESI	electrospray ionization
et al.	*et alia* (and others)
EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s)
Gal*f*	galactofuranose
GalT's	galactofuranosyltransferases
Gal*p*	galactopyranose
GlcNAc	*N*-Acetylglucosamine
h	hour(s)
HIV	human immune deficiency virus
HRMS	high resolution mass spectrometry

HPLC	high performance liquid chromatography
HMBC	heteronuclear multiple bond correlation spectroscopy
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	Hertz
INH	isoniazid
IR	infrared
J	coupling constant
K_i	inhibitor constant
L	litre
LAM	lipoarabinomannan
Log P	logarithm partition coefficient
LM	lipomannan
LB	lysogeny broth
LB/T	lysogeny broth/tween
lit.	literature
M	molar
m	multiplet (in NMR)
m	meta
m.p.	melting point
m/z	mass/charge ratio
M^+	molecular mass ion
Man	mannose
mAGP	mycolylarabinogalctan peptodooglycan
Man*p*	mannopyranose
ManLAM	mannan capped lipoarabinomannan
mbar	millibar
M. bovis	*Mycobacterium bovis*
m-CPBA	3-chloroperbenzoic acid
MDR-TB	multidrug resistant tuberculosis
Me	methyl
MeCN	acetonitrile
MeOH	methanol

mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
mM	millimolar
mmol	millimole
mol	mole
mol. sieves	molecular sieves
MPI anchor	mannosyl phosphate inositol anchor
M. smegmatis	*Mycobacterium smegmatis*
MS	mass spectrometry
M. tuberculosis	*Mycobacterium tuberculosis*
NADH	nicotinamide adenine dinucleotide hydride
NeuAc	*N*-acetylneuraminic acid
nm	nanometer
nmol	nanomole
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
O/N	overnight
OD_{600}	optical density of a sample measured at wavelength of 600 nm
p	para
Pd/C	palladium on carbon
PDB	protein data bank
PEG	polyethylene glycol
Ph	phenyl
ppm	parts per million
pRpp	5-phosphoribosyl-1-pyrophosphate
p-TSA	*para*-toluenesulfonic acid
py	pyridine
PZA	pyrazinamide
q	quartet (in NMR)

quant.	quantitative
R	generic organic group, unless specified
RIF	rifampicin
R_f	retention factor
RMSD	root-mean-square deviation
RP-HPLC	reverse phase high performance liquid chromatography
rpm	revolutions per minute
rt	room temperature
s	singlet (in NMR)
sec	second(s)
t	tertiary
t	triplet (in NMR)
TB	tuberculosis
TBS	*tert*-butyldimethyl silyl ether
TBAF	*tert*-*n*-butylammonium fluoride
TDR-TB	total drug resistant tuberculosis
TEA	triethylamine
TEG	triethylene glycol
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TMPK*mt*	thymidine monophosphatekinase *Mycobacterium tuberculosis*
$TMSN_3$	trimethyl silyl azide
TrCl	tritylchloride
UDP-Gal*f*	uridine diphosphate galactofuranose
UGM	UDP-galactopyranosemutase
UV	ultraviolet
v/v	volume by volume
w/v	weight by volume
XDR-TB	extensively drug resistant tuberculosis
XP	extra precision

Amino acids:

Asp	Aspartic acid
Glu	Glutamic acid
Phe	Phenylalanine
Asn	Asparagine
Pro	Proline
Gln	Glutamine
Arg	Arginine
Val	Valine
Trp	Tryptophan
Tyr	Tyrosine

Chapter 1 Introduction

1.1 General introduction

Tuberculosis (TB) is one of the primary infectious diseases worldwide, especially in developing countries. *Mycobacterium tuberculosis* is recognised as the causative agent for TB.[1] TB has existed since ancient times and remains a major threat to human health; up to one-third of the world's population is latently infected and 10.4 million new cases and 1.4 million deaths were reported in 2016.[2] People infected by Human Immune deficiency Virus (HIV) are at an especially high risk of contracting TB due to their compromised immune system. In many countries, the rate of increase of infection is exacerbated by both poor public health and apparent synergism with HIV.[2,3] The resurgence of the disease has prompted interest in increasing understanding of the disease and the development of new anti-mycobacterial agents against drug-resistant tuberculosis.

1.2 Biological background

1.2.1 General aspects of tuberculosis

TB is an infectious disease primarily affecting the lungs, but it can infect and damage the other organs such as the kidneys and heart.[2] *M. tuberculosis* infections can be either of an active or latent form; people with active TB show all the signs and symptoms, such as fever, weight loss, and a cough that last for more than two weeks, and can pass the bacteria to others through air.[4,5] Latent TB bacteria are inactive, but remain alive in the body and become active later. Reactivation of latent TB is a high risk factor for disease development, particularly those co-infected with HIV.

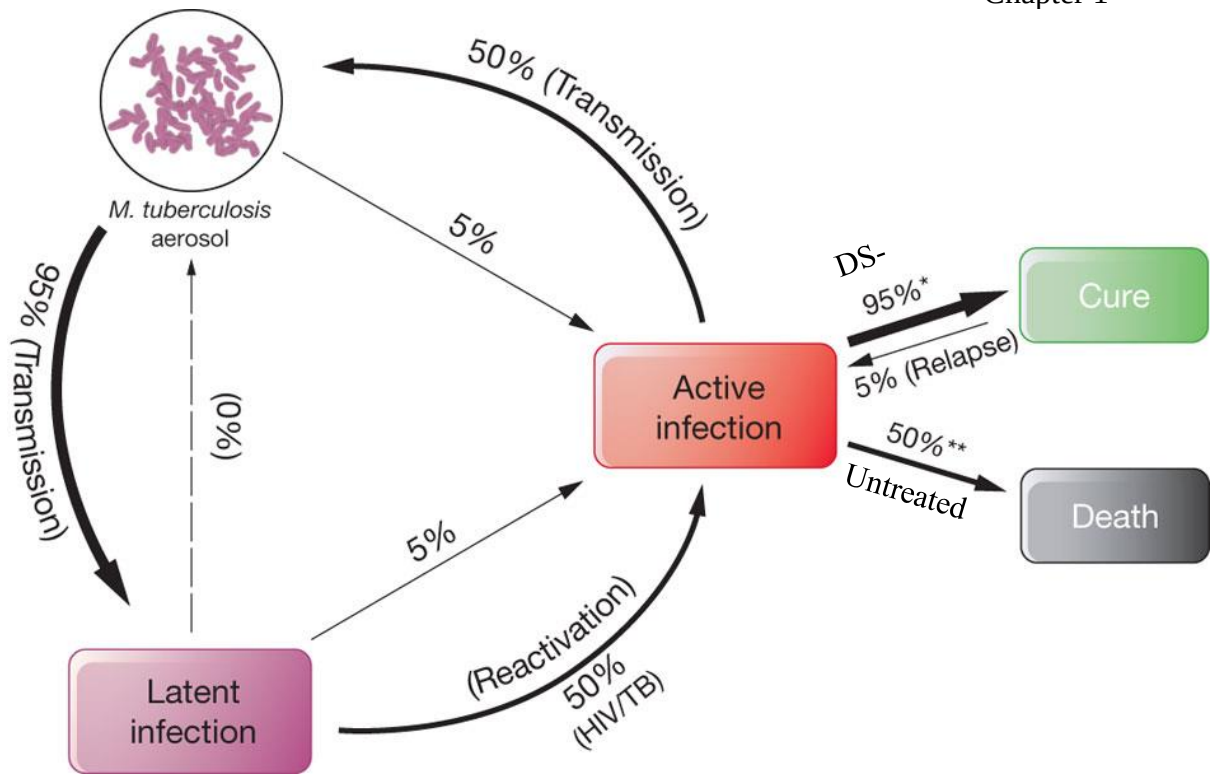


Figure 1.1 Infection stages of *M. tuberculosis*. Adapted from Koul *et al.*[3]

Latent TB is not infectious; approximately only 5% of these patients will go on to develop the active form of the disease by immune suppression, as in the case of HIV. Up to 95% of the people with drug-susceptible TB (DS-TB) recover upon treatment, whereas 5% relapse. If untreated high mortality results (**Figure 1.1**).[3]

A typical current anti-TB treatment involves isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) for the first 2 months, followed by INH and RIF for a further 4 months (**Figure 1.2**).[2,6,7] The emergence and spread of drug resistant strains, namely multidrug-resistant (MDR), extensively drug resistant (XDR), and totally drug-resistant (TDR-TB) strains, has become a major global issue.[2,8,9] MDR-TB is defined as a TB infection that expresses resistance to the first-line anti-TB drugs, INH and RIF. Treatments for MDR infections are significantly more difficult, expensive, and have considerable side effects.

XDR-TB is resistant to INH and RIF, as well as resistant to fluoroquinolones and to any one of the following second-line injectable drugs: amikacin, capreomycin, or kanamycin.[10] Moreover, recently TDR-TB has emerged which is resistant to all current anti-TB drugs. Cases of TDR-TB have become prevalent in China, India, Africa, and Eastern Europe. The biomolecular targets and mode of action of the first-line anti-TB drugs are shown in **Table 1.1**.[11]

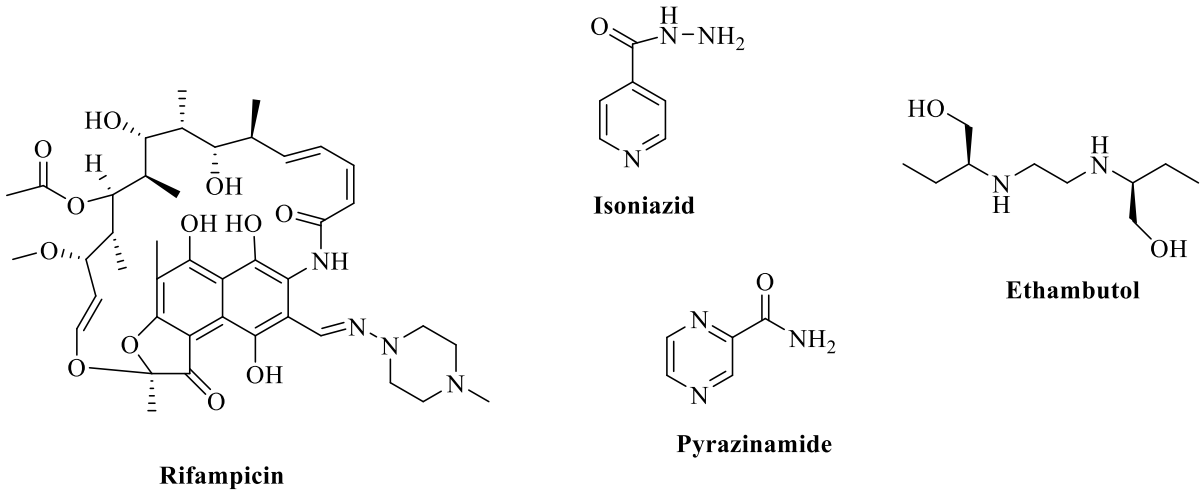


Figure 1.2 First-line anti-TB drugs.

Anti-TB drugs	Target	Mode of action
Isoniazid	Enoyl-acyl carrier protein reductase	Inhibits cell wall mycolic acid biosynthesis
Rifampicin	β subunit of RNA polymerase	Inhibits RNA synthesis
Pyrazinamide	Fatty acid synthase	Inhibits protein translation and membrane energetics
Ethambutol	Arabinofuranosyltransferases	Inhibits cell-wall arabinogalactan synthesis

Table 1.1 Biomolecular targets and mode of action of existing *Mtb* drugs[11]

Recently, the World Health Organisation (WHO) has reclassified the anti-TB drugs into five groups (**Table 1.2**),[2] based on data for safety, efficacy, administration, and drug class. Currently, first-line drugs (Group 1) have been recommended in four-drug combinations, and group 2, 3, and 4 (second-line drugs) are reserved for the treatment of drug resistant TB. Group 5 (third-line drugs) have undefined roles or unclear efficacy with long-term safety concerns.

Group	Drugs
Group 1. First-line oral agents	Isoniazid Rifampicin Ethambutol Pyrazinamide Rifabutin Rifapentine
Group 2. Injectable drugs	Streptomycin Kanamycin Amikacin Capreomycin
Group 3. Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin
Group 4. Oral bacteriostatic second-line drugs	Ethionamide Prothionamide Cycloserine Terizidone *para*-aminosalicylic acid
Group 5. Drugs with limited data on efficacy and long-term safety issues	Bedaquiline Delamanid Linezolid Clofazimine Amoxicillin/ clavulanate Imipenem/cilastatin Thioacetazone Clarithromycin

Table 1.2 The WHO classification of anti-TB drugs.[2,12]

The emergence of drug resistant strains of *M. tuberculosis* is caused mainly by inappropriate use of antimicrobial drugs, premature treatment interruption and use of ineffective drug formulations. Historically, the cell wall structure of *M. tuberculosis* is well understood and it has been an effective target for many drugs. However the multi-layered, hydrophobic nature of the cell envelope results in low cellular permeability and acts as a barrier against hydrophilic antibacterial drugs.

1.2.2 Cell wall structure of *M. tuberculosis*

The mycobacterial cell wall (**Figure 1.3**) is composed of carbohydrate-containing molecules such as polysaccharides and glycolipids.[13]

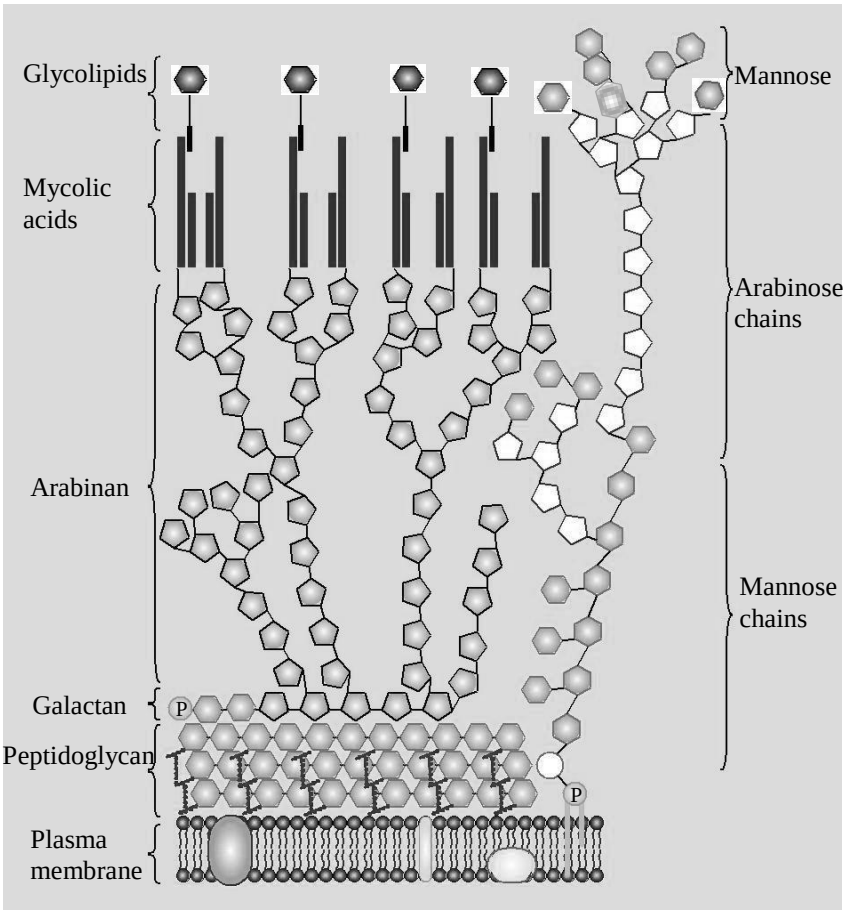


Figure 1.3 Schematic representation of the mycobacterial cell wall. Adapted from Besra *et al.*[14]

The two major cell wall oligosaccharides, lipoarabinomannan (LAM) and arabinogalactan (AG), are essential to mycobacterial survival and growth.[13,15] The AG complex consists of a polymer of galactofuranose (Gal*f*) and an Ara*f* residue covalently linked to the peptidoglycan at the reducing end by way of an α-L-Rha-(1→3)-α-GlcNAc-OPO_3 diglycosylphosphoryl bridge,[16] and is esterified at the non-reducing end with mycolic acids; the complex is called mycolylarabinogalactan-peptidoglycan (mAGP).[17] Peptidoglycan consists of a polymer formed from alternating units of *N*-acetylglucosamine and *N*-glycolylmuramic acid (**Figure 1.4**).[18] Tetrapeptide side chains are attached to *N*-glycolylmuramic acid, and cross-linked to the polysaccharide chain (AG) *via* phosphodiester links to some of the muramic acid residues at position 6 (**Figure 1.5**).[19]

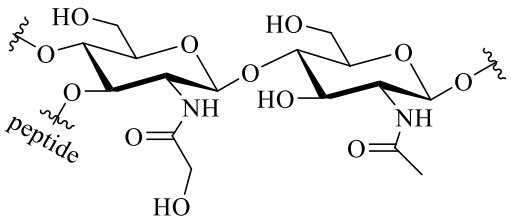


Figure 1.4 *N*-Acetylglucosamine and *N*-glycolylmuramic acid in the peptidoglycan

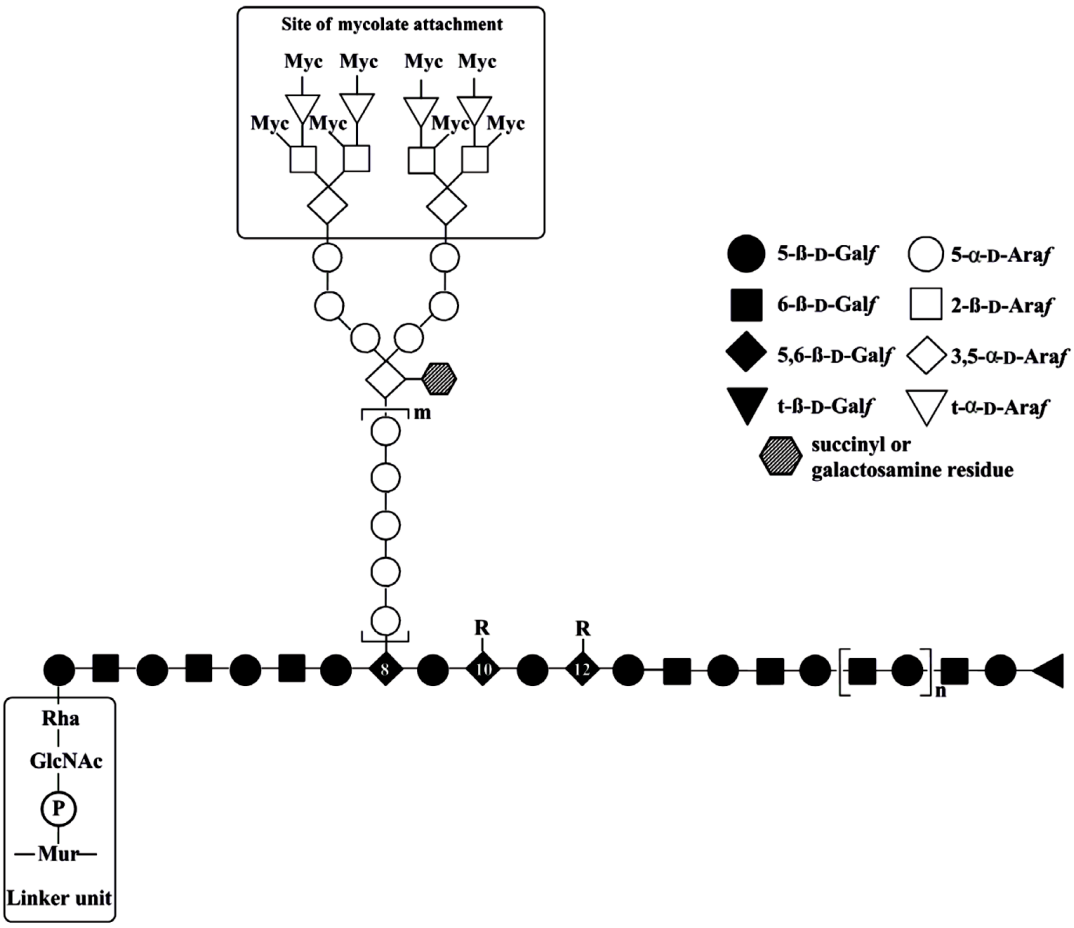


Figure 1.5 The general structure of Arabinogalactan. Adapted from Besra *et al.*[14]

An unusual structural feature of these glycans is that all of the arabinose and galactose residues are in the furanose ring form.[20] The galactan component of AG is made up of approximately 30 Gal*f* residues with alternating β-(1→5) and β-(1→6) linkages combined in a linear fashion. Approximately 70 Ara*f* residues are linked to the linear galactan backbone at the position 5 of some of the β-(1→6) linked Gal*f* residues.[21,17] The majority of the arabinan chains are composed of α-5-linked α-D-Ara*f* residues with branching introduced by 3,5-α-D-Ara*f* linked residues (**Figure 1.5**).[22] The non-reducing termini of the arabinan chains have a [β-D-Ara*f*-(1→2)-α-D-Ara*f*]$_2$-3,5-α-D-

Ara*f*-(1→5)-α-D-Ara*f* hexa-arabinofuranosyl motif (**Figure 1.6**).[17,23] Mycolic acids (long-chain α-alkyl β-hydroxy fatty acids) are attached in clusters of four on two-thirds of the terminal arabinofuranosyl hexasaccharide by ester linkages.[24]

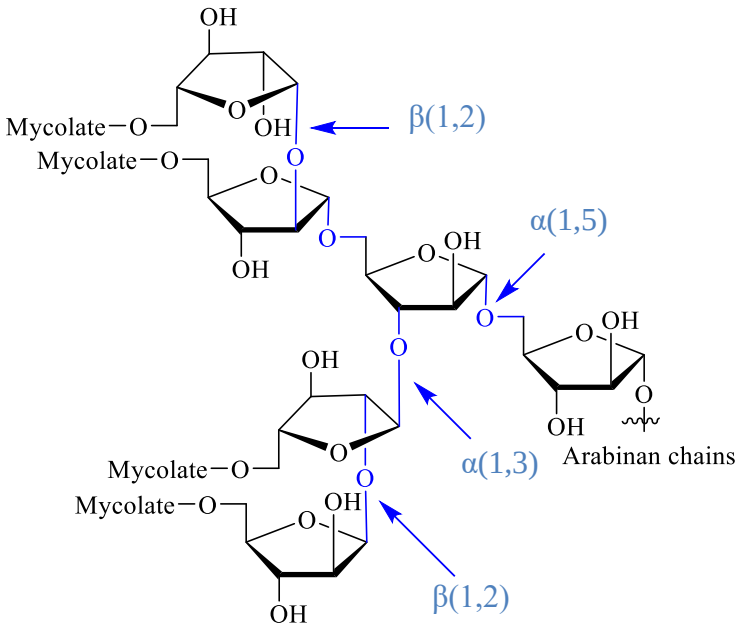


Figure 1.6 Structure of the non-reducing terminus hexa-arabinofuranosyl motif.

LAM is a polymer of mannopyranose (Man*p*) and arabinofuranose (Ara*f*) residues, and is the extended form of lipomannan (LM). It is non-covalently attached to the plasma membrane by the lipid portion of a Mannosyl phosphate inositol anchor (MPI anchor, **Figure 1.7**).[25,26]

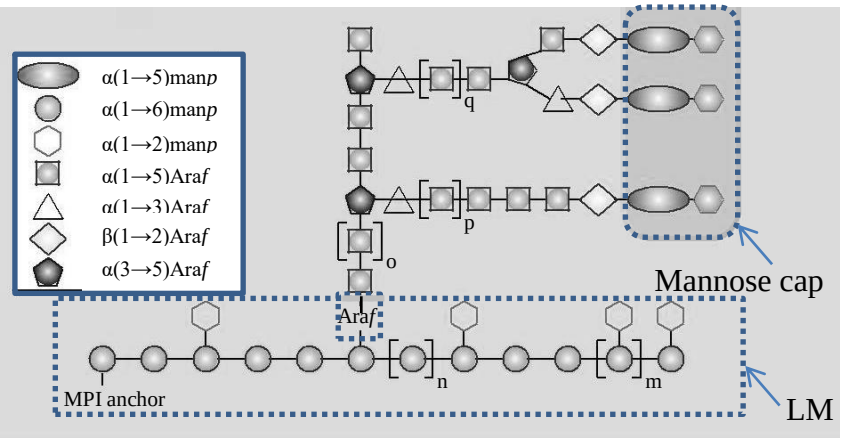


Figure 1.7 The general structure of LAM. Adapted from Besra *et al.*[14]

The backbone, common to both LAM and LM, contains linear α-(1→6) mannosyl residues (21-34 Man*p* residues) linked with 5-10 units of single α-(1→2) mannopyranosyl side chains. In the case of LAM, the mannan is linked to an arabinan polymer, containing approximately 55-70 Ara*f* residues with α-(1→5) linkages.[27,28] The arabinan termini of LAM, isolated from *M. tuberculosis* are extensively capped with manno-oligosaccharides, contains mono-, di-, and tri- α-(1→2)-D-Man*p*, and are called ManLAM.[29]

1.2.3 Arabinan biosynthesis

The structure of the mycolic acid-arabinogalactan-peptidoglycan complex of *M. tuberculosis* is fairly well understood. However, identification and isolation of enzymes for the biosynthesis of the cell envelope are crucial to eradicate the drug resistance strains. The biosynthesis of the mycobacterial cell wall requires several different sugar-processing enzymes. Glycosyltransferases, for example mannopyranosyl transferases (ManP's), galactofuranosyl transferase (GalT's) s and

arabinofuranosyltransferases (AraT's), are responsible for the assembly of the glycans.[30] The ManP's and GalT's are involved in the biosynthesis of LAM and galactan respectively. The biosynthesis of this arabinan is postulated to involve a family of AraT's that produce β-(1→2), α-(1→3), and α-(1→5) arabinofuranosyl linkages.

1.2.3.1 Arabinofuranosylsyltransferases

For both AG and LAM, several arabinofuranosyltransferases (AraT's) are involved in arabinan biosynthesis. These enzymes belong to two characterized classes of enzymes: Emb (EmbA, EmbB, and EmbC), and Aft (AftA, AftB, AftC, and AftD). None of the arabinofuranosyltransferases (AraT's) have been successfully expressed. However, the AraTs have been identified through arabinofuranosyltransferase assays (cell free-assays) using mycobacterial cell wall preparations and synthetic arabinan acceptors.[31,32,33] Individual genetic disruption of Emb proteins in *M. smegmatis* revealed that both EmbA and EmbB are involved in the formation of the hexa-arabinofuranosyl motif of AG,[34,35] whereas EmbC is involved in the elongation of the arabinan portion of LAM.[36] *In vitro* assays using cell wall galactan as an acceptor demonstrated AftA is required for the transfer of the first Ara*f* to the galactan domain of AG.[37] Deletion studies of AftB and AftC in *M. smegmatis* revealed that are involved in the terminal β-(1→2) capping[38] and internal α-(1→3) branching[39] of AG respectively. *In vitro a*ssays using cell-free extracts from *M. smegmatis* demonstrated AftD is involved in the internal α-(1→3) branching on linear α-(1→5) linked neoglycolipid acceptors of both AG and LAM (**Figure 1.8**).[40]

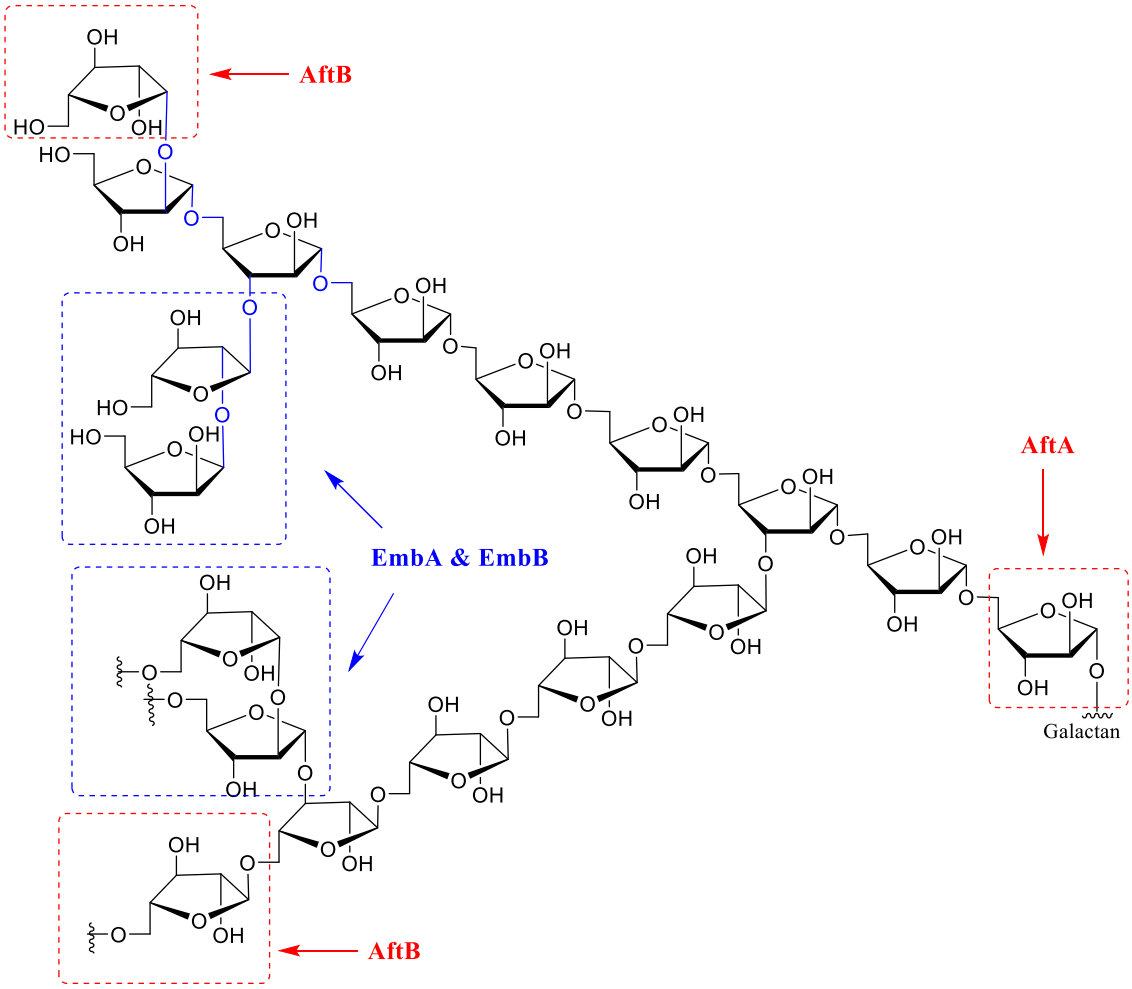


Figure 1.8 The roles of arabinofuranosyltransferases (AraT's) in arabinan biosynthesis[41]

A typical AraT-catalyzed reaction (**Figure 1.9**) involves the coupling of an oligosaccharide acceptor with decaprenolphosphoarabinose (DPA) to afford an elongated oligosaccharide.[32, 42,43] The polysaccharide AG is assembled as a polyprenol diphosphate intermediate (polyprenol-P-P-GlcNAc), which is then attached to peptidoglycan prior to the esterification of the non-reducing termini with the mycolic acids.

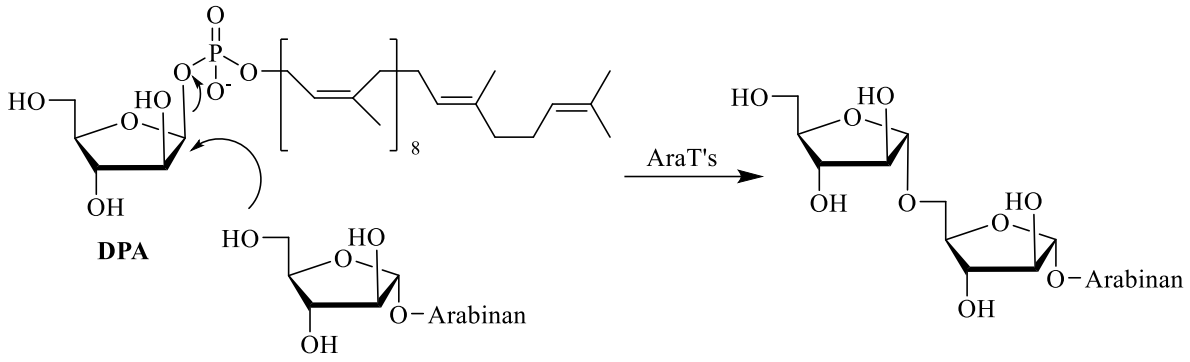


Figure 1.9 Typical AraT's catalysed reaction for arabinan biosynthesis.

The biosynthesis of DPA begins with 5-phosphoribosyl-1-pyrophosphate **1.1** (pRpp) which is converted to decaprenylphosphoryl-5-phosphoribose **1.2** (DPPR), in a reaction catalysed by decaprenylphosphoryl-5-phosphoribose synthase (Rv3806c), which is then dephosphorylated by a phosphatase to give decaprenylphosphoryl ribose **1.3** (DPR). Subsequently, DPR is epimerized to DPA **1.5**. Crick *et al.* initially proposed that this epimerization occurs *via* an oxidation-reduction process catalysed by two enzymes;[44] DprE1 (Rv3790), which functions as a decaprenylphosphoryl-β-D-ribose oxidase, and DprE2 (Rv3791), which functions as a decaprenylphosphoryl-D-2-keto-erythropentose reductase.[45] Interestingly, Meniche *et al.* have reported that a third enzyme (Rv2073c) may also be involved the epimerization process (**Figure 1.10**).[46]

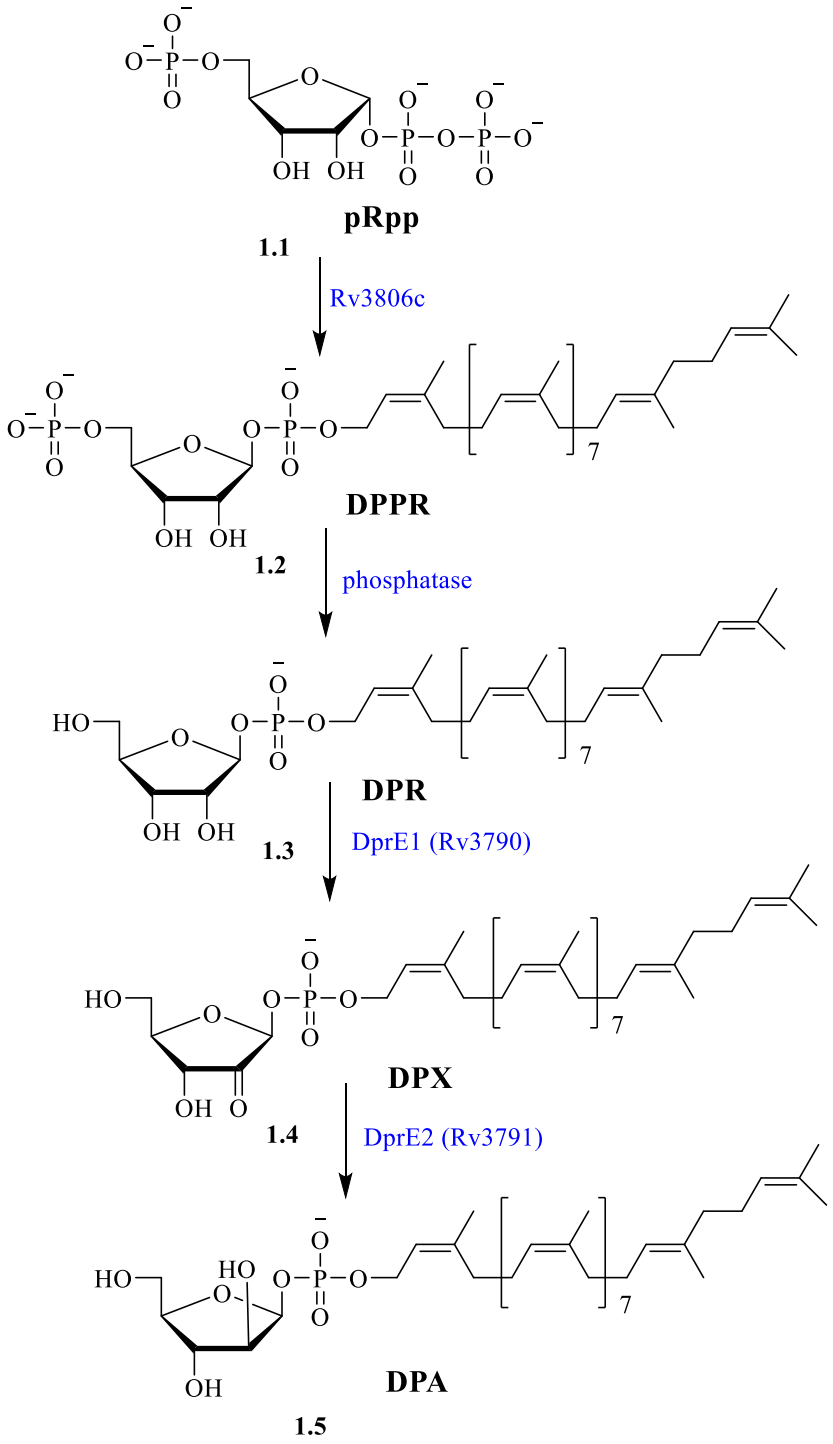


Figure 1.10 The biosynthesis of DPA from pRpp[46]

As discussed earlier, the structures of the cell wall are unique to mycobacteria and are crucial to mycobacterial viability. Inhibition of the biosynthesis of the polysaccharide of the cell wall, therefore represents an attractive target for the development of anti-

TB agents. Previous studies have attempted inhibition of various glycosyl transferases,[47,48,49] and of the Gal*p*/Gal*f* mutase enzyme involved in the isomerization of pyranose/furanose during the assembly of the galactan cell wall component.[50,51,52,53,54] In particular, the discovery of metabolically stable analogues of DPA which may act as potent inhibitors of AraT's is an attractive strategy for drug development.

1.3 The design of DPA analogues as inhibitors of arabinofuranosyltransferases

A particular advantage of developing analogues of DPA as therapeutic agents is that glycoconjugates of arabinofuranose and galactofuranose are not found in mammals, which means such compounds should not interfere with normal mammalian sugar processing *in vivo*. Therefore, such arabinose residues may be predicted to have no toxic side effects to mammalian cells, which mean that a higher dosage could be used to exterminate infection and also to reduce the treatment periods; another desirable advance as current treatment takes approximately six months.[55,56] A further advantage of this approach is that it should be possible to fine-tune the pharmacokinetic properties of any lead drug candidate because there is ample scope for structural modification of the basic DPA skeleton.

The pharmacokinetic properties of drugs are crucial for their absorption, distribution, metabolism and excretion in the human body. The properties have been derived by 'Lipinski's rule of 5'. These rules conclude that an orally active drug is more likely to be membrane permeable and easily absorbed by the body if it matches the following criteria: [57,58]

- The molecular weight of the compound is less than 500 Daltons.

- The octanol-water partition coefficient of the compound (logP) is less than 5.
- Not more than five hydrogen bond donors.
- Not more than ten hydrogen bond acceptors.

Tuning of these properties is important for the effective development of a medicine since molecular features such as hydrophobicity are important in terms of metabolic processing of a drug when administered in humans. Thus, the eventual optimisation of a lead-DPA analogue into an effective orally bioavailable drug may be easier to achieve than for other alternative molecular targets. The DPA donor analogues could be expected to be potent anti-mycobacterial agents because DPA is a substrate for many AraT's, and these compounds are therefore expected to inhibit several enzymes, in the same way that EMB targets two or more Emb proteins. Analogues of DPA would be expected to block a number of biosynthetic steps, unlike analogues of the glycosyl acceptors each of which is recognized by a specific AraT.

In order to design mimics of DPA the replacement of the highly polar labile glycosyl phosphate and the hydrophobic decaprenyl moiety with a suitable isostere is required.[59,60] A significant number of examples have been previously reported by the Lowary *et al.*[42,61,62], Fairbanks group,[63,64] and several others[65] for the isosteric replacement of glycosyl phosphate, such as using phosphonates **1.6**,[42] phosphinic acids **1.7**,[61] sulfones **1.8**[61] and **1.9**,[64] triazoles **1.10**,[63] sulphonamides **1.11** and sufenamides **1.12.**[65] Recently, Legentil *et al.*[66] developed galactofuranosidesderivatives **1.13** which lack a phosphate or phosphate isostere, yet which displayed moderate inhibitory activity (**Figure 1.11**).

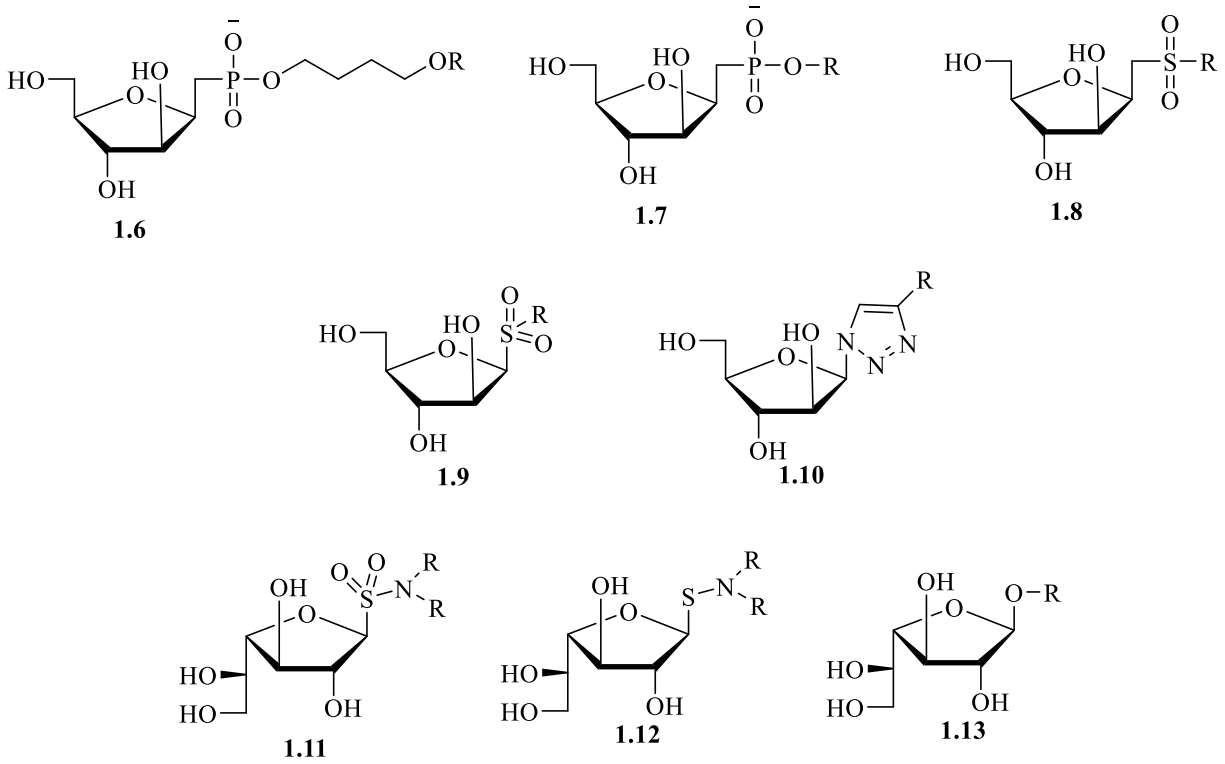
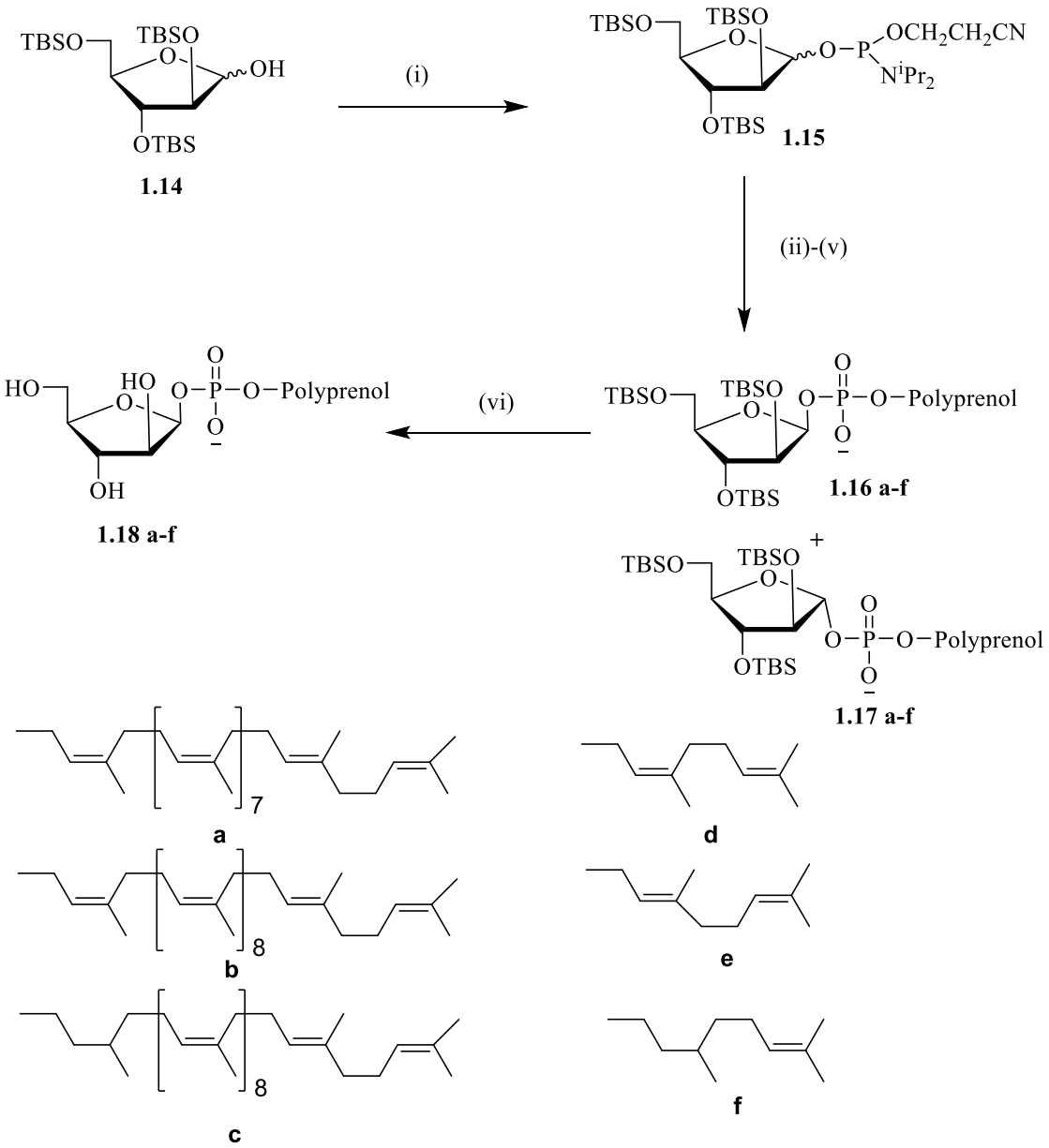


Figure 1.11 Decaprenylphosphoarabino and galactofuranose analogues reported by Fairbanks et al. and others.

Anti-mycobacterial activities of these stable DPA analogues are presumed to arise from inhibition of AraT's, and thus inhibition of cell wall biosynthesis, which affects mycobacterial growth and survival. In fact, the currently used antibiotics ethambutol (MIC >4 μg/mL)[67] and isoniazid (MIC 0.1 μg/mL) block cell wall assembly.[68] MIC stands for the minimum inhibitory concentration, and is the lowest concentration of antimicrobial drug that inhibit the visible growth of the mycobacteria: the lower the MIC the more potent the compound is against the bacterium. MIC values are typically determined by using a microplate "Alamar Blue" assay (AB). The AB assay is a rapid, inexpensive, and high-throughput assay for antimycobacterial drug screening.[69]

Besra *et al.*[31] reported a series of DPA analogues **1.18 a-f** with varying lengths of prenyl side chains, which were synthesized as shown in **Scheme 1.1**.

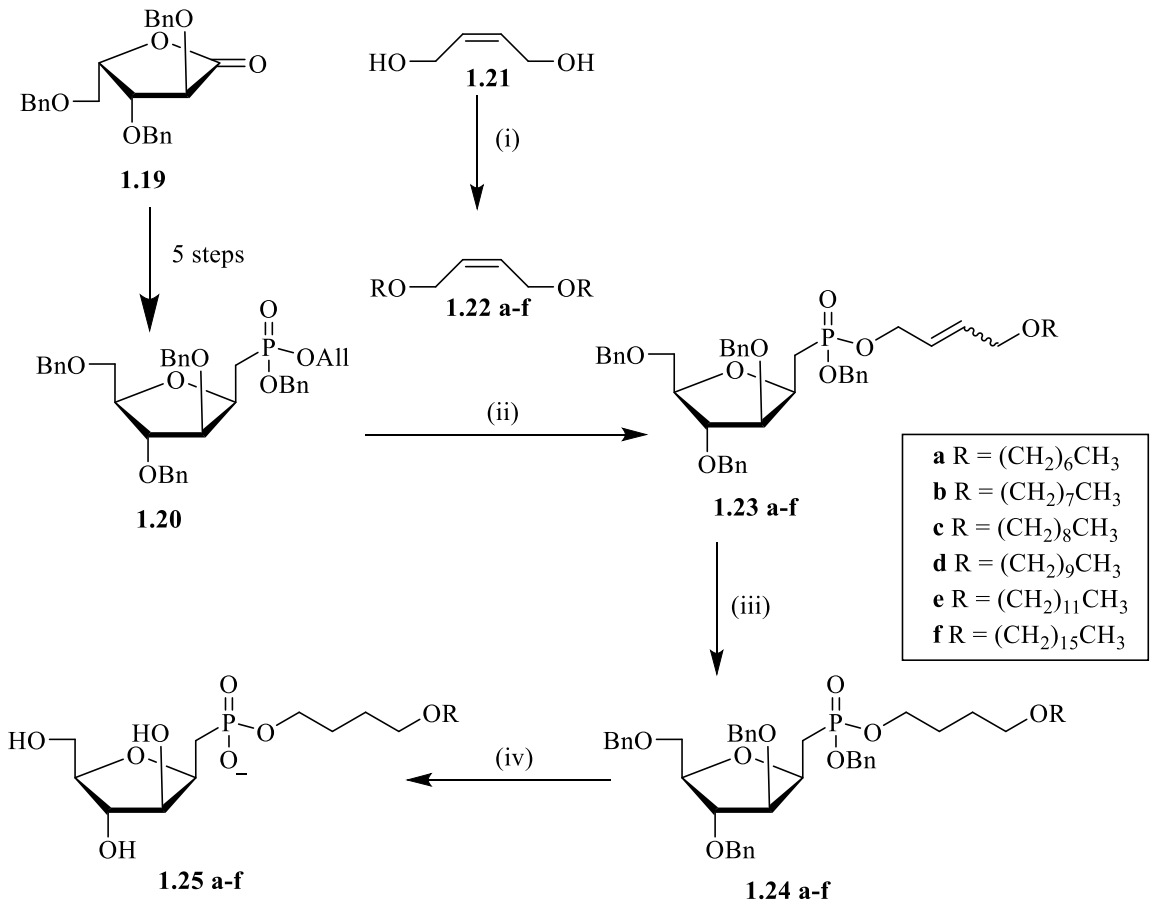


Scheme 1.1 The synthesis of prenylphosphoarabinofuranoside DPA analogues **1.18a-f** by Besra *et al.*[31]; (i) 2-cyanoethyl-*N*,*N*-diisopropylchlorophosphorylamidite, EtN^iPr_2, DCM, -78 °C; (ii) Polyprenol **a-f,** tetrazole; (iii) H_2O_2, THF; (iv) KOH, MeOH; (v) Separate by SiO_2; (vi) NH_4OH, MeOH.

The synthesis of **1.15** was achieved by the reaction of 2-cyanoethyl *N*,*N*-diisopropylchlorophosphorylamidite and protected arabinose **1.14**. Various polyprenols were coupled to **1.15** using tetrazole activation, creating a mixture of

anomers which were separated by chromatography (**1.16a-f** and **1.17a-f**) after oxidation and base deprotection. The final deprotection of the β-anomers **1.16a-f** yielded prenylphosphoarabinose **1.18a-f**. The β-anomers **1.18a-f** were tested using an AraT's assay (cell free assay). It was found that only long-chain prenyl chains **1.18a-c** were recognized as arabinose donor by the active site of AraT's. Thus it was suggested that hydrophobicity of the side chain plays a vital role in substrate recognition.

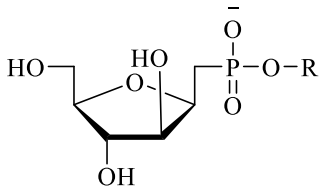
In 2002, Lowary *et al.*[42] synthesized a series of C-phosphonate analogues **1.25a-f** as shown in **Scheme 1.2**.



Scheme 1.2 Synthesis of C-phosphonate analogues of DPA **1.25a-f** by Lowary *et al.*[42]; (i) NaH, RI, DMF, rt; (ii) **1.22a-f**, Grubbs catalyst, DCM, 40 °C; (iii) KOC(O)N=NC(O)OK, AcOH, MeOH, 40 °C; (iv) H_2, Pd/C, MeOH, rt.

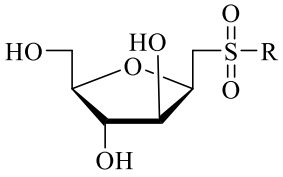
The analogues **1.23a-f** were achieved by an olefin cross metathesis reaction between C-phosphonate **1.20** and a series of alkenes **1.22a-f** using Grubbs catalyst. The C-phosphonate **1.20** was obtained from lactone **1.19** in five steps. The alkenes **1.22a-f** were synthesized from alcohol **1.21** under standard alkylation conditions. The alkene of C-phosphonate analogues **1.23a-f** was reduced and subsequent catalytic hydrogenation afforded the target compounds **1.25a-f**. The C-phosphonate analogues **1.25a-f** were then tested against *M. tuberculosis* using an AB assay. Compound **1.25f** displayed promising anti-mycobacterial activity (3.13 µg/mL). However, compounds **1.25a-1.25e** failed to inhibit mycobacterial growth.

Given this success, a series of C-phosphonic acid **1.26a-e** and glycosyl sulfone **1.27a-g** analogues (**Figure 1.12**) were also synthesized by Lowary *et al.* [61]



1.26a-e

a R = $(CH_2)_7CH_3$
b R = $(CH_2)_9CH_3$
c R = $(CH_2)_{11}CH_3$
d R = $(CH_2)_{15}CH_3$
e R = $(CH_2)_{19}CH_3$

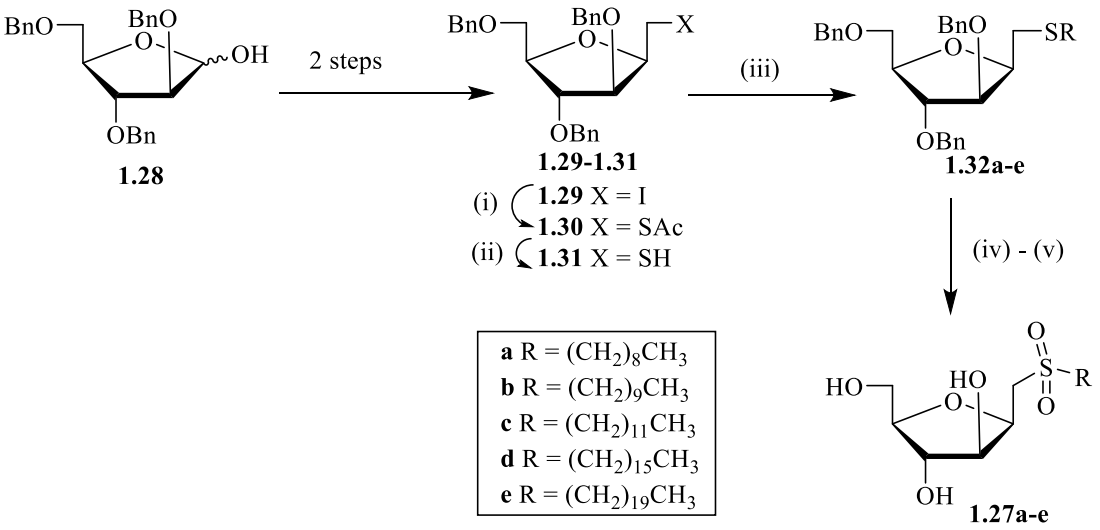


1.27a-g

a R = $(CH_2)_8CH_3$
b R = $(CH_2)_9CH_3$
c R = $(CH_2)_{11}CH_3$
d R = $(CH_2)_{15}CH_3$
e R = $(CH_2)_{19}CH_3$
f R = $(CH_2)_{10}O(CH_2)_{15}CH_3$
g R = $(CH_2)_2CH(CH_3)(CH_2)_3CH(CH_3)_2$

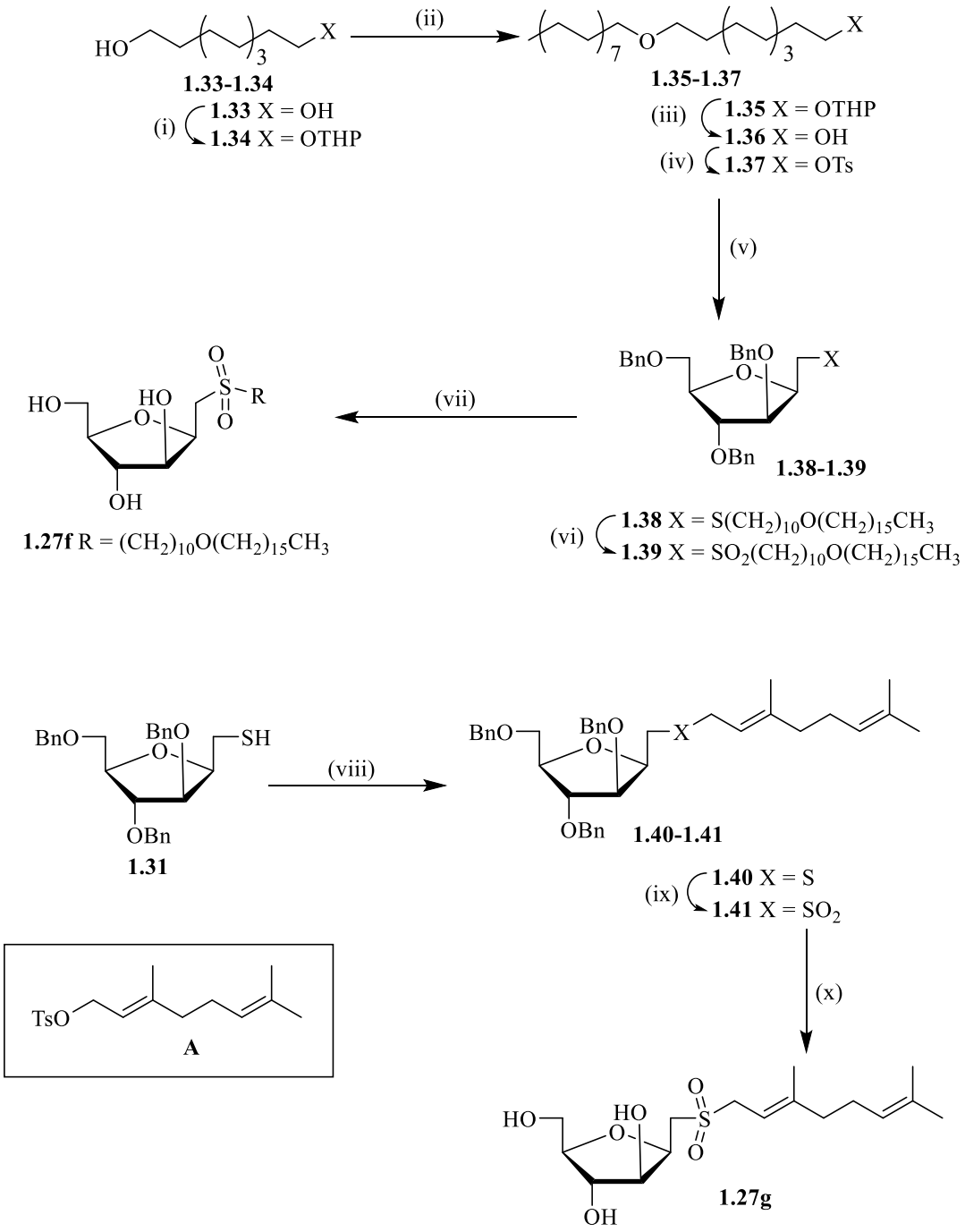
Figure 1.12 Glycosyl sulfones and C-phosphonic acid as DPA analogues[61]

The synthesis of the series of glycosyl sulfones is shown in **Scheme1.3** and **Scheme 1.4**.



Scheme 1.3 Synthesis of glycosyl sulfones **1.27a-e** by Lowary *et al.*; (i) KSAc, DMF, rt; (ii) $LiAlH_4$, Et_2O, rt; (iii) For **1.32a, c & d**: RI, NaH, DMF, rt; For **1.32b**: RI, *n*-BuLi, Et_2O, 0 °C to rt; For **1.32e**: $TsO(CH_2)_{19}CH_3$, *n*-BuLi, THF, 0 °C to rt; (iv) m-CPBA, DCM, rt; (v) H_2, Pd/C, MeOH, AcOH.

The glycosyl sulfones **1.27a-d** were synthesized from iodide **1.29**, which was prepared in two steps from commercially available arabinose **1.28**. The reaction of iodide **1.29** with thioacetate yielded **1.30**. Subsequent deacylation, alkylation, oxidation and catalytic hydrogenation afforded glycosyl sulfones **1.27a-e** (**Scheme 1.3**).



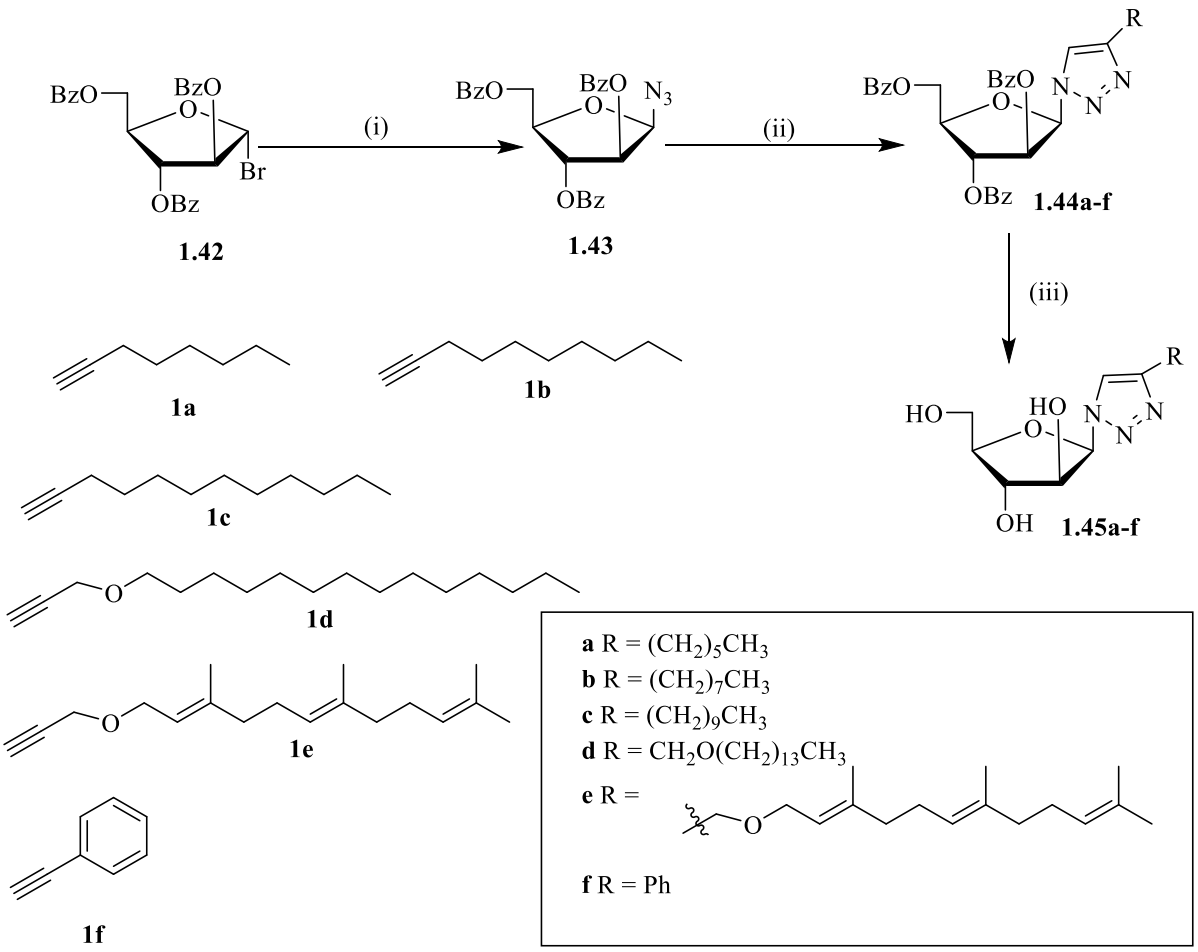
Scheme 1.4 Synthesis of glycosyl sulfones **1.27f-g** by Lowary *et al.*[61]; (i) 3,4-dihydropyran, *p*-TsOH, THF, rt; (ii) $CH_3(CH_2)_{15}I$, NaH, DMF, rt; (iii) AcOH, THF, H_2O, 65 °C; (iv) *p*-TsCl, KH, 18-crown-6, THF, rt; (v) **1.31**, KH, 18-crown-6, THF, rt; (vi) *m*-CPBA, DCM, rt; (vii) H_2, Pd/C, MeOH, AcOH, rt; (viii) **A**, *n*-BuLi, THF; (ix) $NaIO_4$, MeOH, H_2O, 70 °C; (x) H_2, Pd/C, MeOH, AcOH, rt.

The synthesis of oxygenated derivative **1.27f** began with commercially available 1,10-decanediol **1.33**, which was selectively protected using 3,4-dihydropyran and *p*-TsOH

to afford mono protected alcohol **1.34**. Subsequent alkylation of alcohol **1.34**, deprotection, and tosylation afforded **1.37**. Tosylate **1.37** was coupled with thiol **1.31** in the presence of KH and 18-crown-6 providing the thioether **1.38**. Oxidation and catalytic hydrogenation yielded the glycosyl sulfone **1.27f** (**Scheme 1.4**). The compound **1.27g** was achieved by alkylation of **1.31,** and subsequent oxidation and catalytic hydrogenation afforded the desired product (**Scheme 1.4**).

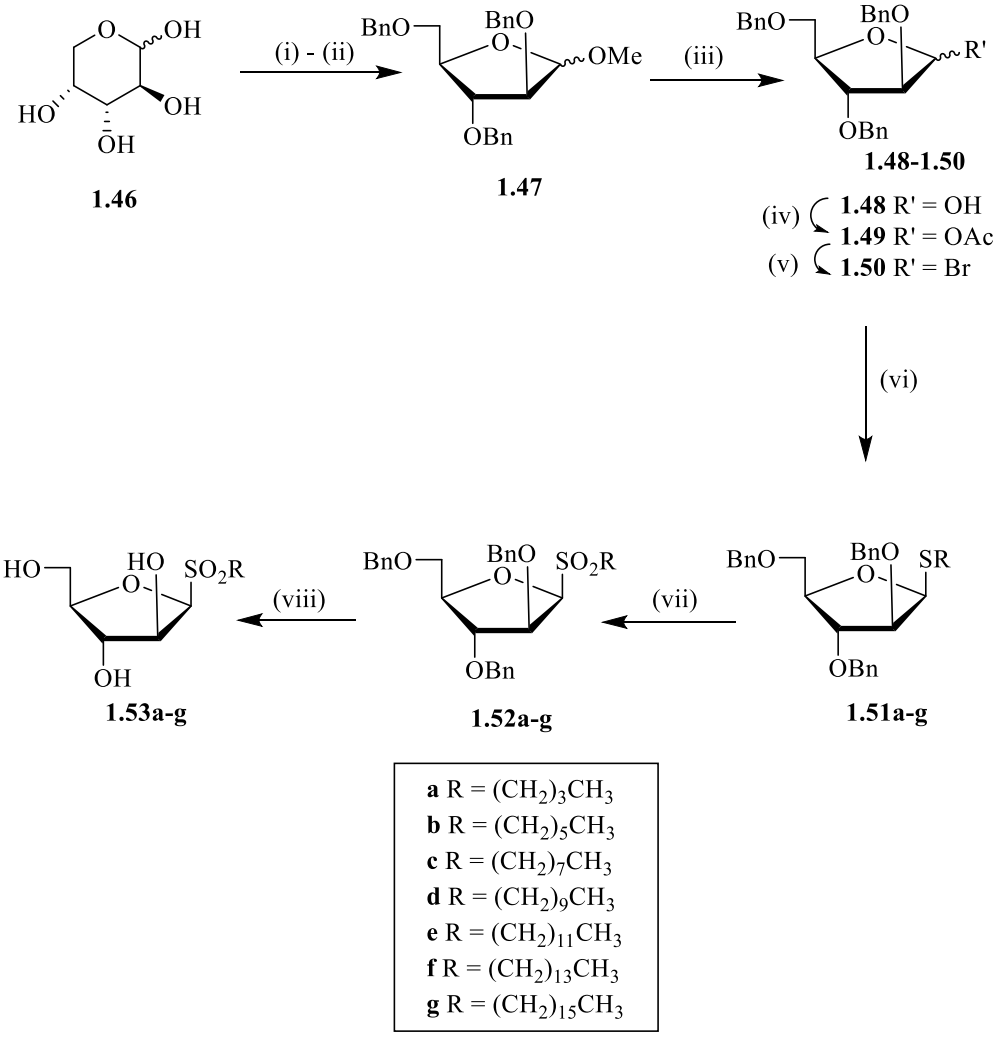
The phosphonic acid **1.26a-e** and glycosylsulfone analogues **1.27a-g** were tested against *M. tuberculosis* ($H_{37}Rv$) using fluorescence based Alamar Blue assay. However, none of the compounds showed a promising activity as C-phosphonate analogue **1.25f**.

Fairbanks *et al.* synthesized a series of glycosyl triazoles **1.45a-f** and glycosyl sulfones **1.48a-g** as shown in **Scheme 1.5** and **Scheme 1.6** respectively.



Scheme 1.5 Synthesis of glycosyl triazoles **1.45a-f** as DPA analogues reported by Fairbanks *et al.*[63]; (i) NaN_3, Bu_4NHSO_4, DCM, $NaHCO_3$ 1:1; (ii) **1a-f**, CuI, DIPEA, 110 °C; (iii) NaOMe, MeOH-THF.

The benzoylated arabinoside **1.42** was reacted with NaN_3 to give the corresponding glycosyl azide **1.43** as an anomeric mixture (α:β, 1:2); the desired β-anomer was separated by flash column chromatography. Cu(I) catalysed Huisgen cycloaddition of azide **1.43** and alkyne **1a-f** in the presence of CuI and diisopropylethylamine (DIPEA) gave the triazole **1.44a-f**. Finally, deprotection with NaOMe yielded desired glycosyl triazoles **1.45a-f** (**Scheme 1.5**).



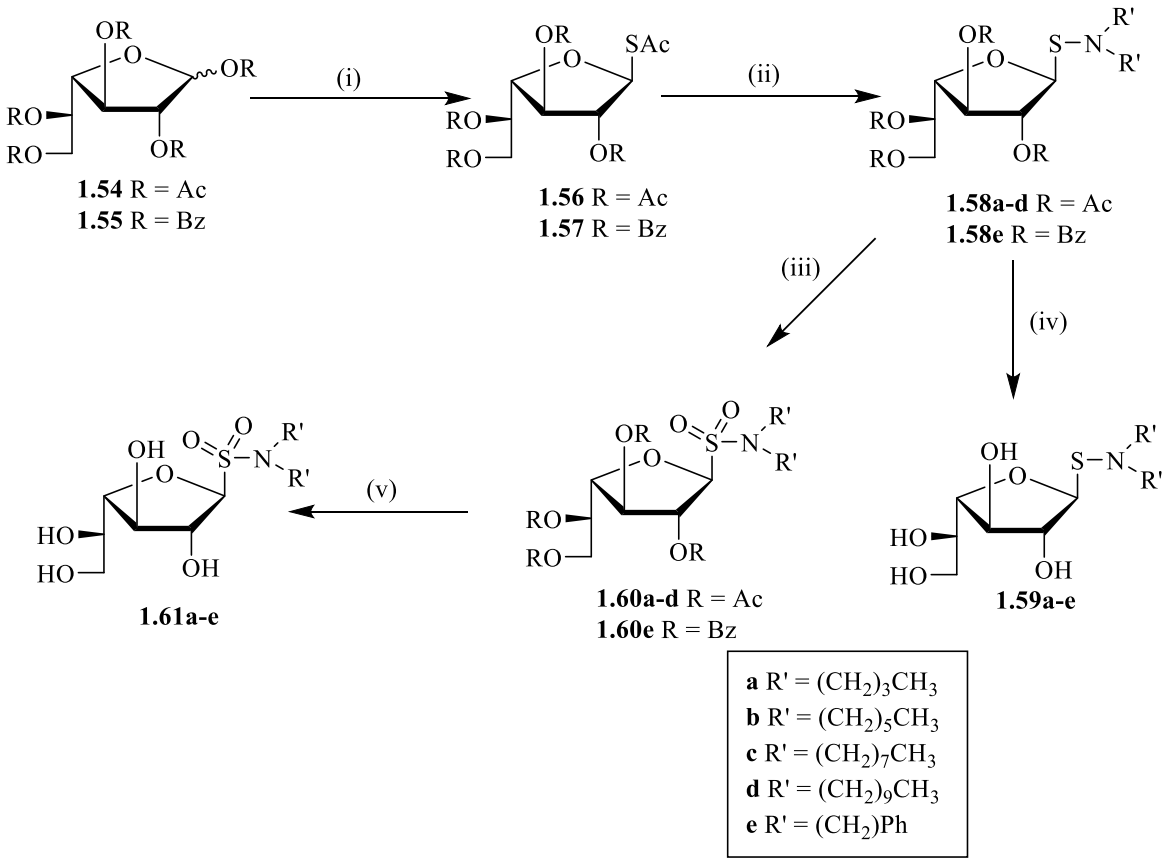
Scheme 1.6 Synthesis of glycosyl sulfones **1.53a-g** as DPA analogues reported by Fairbanks *et al.*[64]; (i) AcCl, MeOH, rt; (ii) NaH, BnBr, DMF, rt; (iii) 80 % AcOH, 115 °C; (iv) Ac_2O, py, rt; (v) TMSBr, DCM, -40 °C to rt; (vi) RSH, 2,4,6-tri-*tert*-butylpyrimidine (TTBP), DCM, rt; (vii) *m*-CPBA, $NaHCO_3$, DCM, rt; (viii) H_2, Pd/C, MeOH, rt.

The synthesis of glycosyl sulfones **1.53a-g** began with D-arabinose, which was treated with acetyl chloride and MeOH to give methyl arabinofuranoside via Fischer glycosylation, which was then benzylated to give fully protected arabinoside **1.47**. Subsequent acid-catalysed hydrolysis, acetylation, and bromination afforded glycosyl bromide **1.50**. The protected glycosyl sulfones **1.51a-g** were prepared by the reaction

of glycosyl bromide and the corresponding thiols in the presence of TTBP. Subsequent oxidation and deprotection afforded glycosyl sulfones **1.53a-g** (**Scheme 1.6**).

The glycosyl triazoles **1.45a-f** and glycosyl sulfones **1.53a-g** were tested against *M. bovis*. Compounds **1.45b**, **1.45e** and **1.53e** displayed moderate anti-mycobacterial activity with MIC of 62 µg/mL. However, compound **1.45d** was more than twice as active (MIC 31 µg/mL). These results demonstrate that the length of the hydrophobic side chain can strongly influence the activity of the compound.

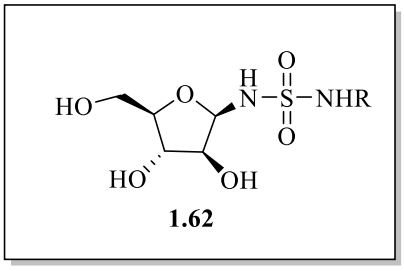
In related work, von Itzstein *et al.* synthesized a series of galactofuranosyl sulfenamides **1.60a-e** and sulfonamides **1.63a-e** as shown in **Scheme 1.7**.



Scheme 1.7 Synthesis of galactofuranosyl sulfonamides and sulfenamides reported by von Itzstein *et al.*[70]; (i) $BF_3.OEt_2$, HSAc, 0 °C to rt or $SnCl_4$, HSAc, 0 °C to rt; (ii) HNR'_2, $BrCH(CO_2Et)_2$, MeOH, rt; (iii) *m*-CPBA, DCM, reflux; (iv) NaOMe, MeOH, rt; (v) NaOMe, MeOH, rt.

As starting materials, tetra-*O*-acetylated **1.54** and benzoylated **1.55** galactofuranoside were reacted with the thioacetic acid in the presence of catalytic $SnCl_4$ or $BF_3.OEt_2$ to provide thioacetate derivatives **1.56** and **1.57** respectively. β-sulfenamides **1.58a-e** were achieved by the reaction of glycosyl thioacetates **1.56** and **1.57** with bromomalonate and corresponding secondary amines, which were then deprotected under Zemplen reaction conditions to give target sulfenamides **1.59a-e**. Oxidation of sulfenamides **1.58a-e** using *m*-CPBA, and subsequent deacetylation (**1.60a-d**) and benzoylation (**1.60e**) yielded sulfonamides **1.61a-e**. The sulfenamide **1.59a-e** and sulfonamide **1.61a-e** derivatives were tested against *M. smegmatis* using AB assay. Sulfenamides **1.59c-d** and sulfonamide **1.61c** displayed strong inhibitory activity against *M. smegmatis* with MICs of 4 µg/mL, 1 µg/mL and 2 µg/mL respectively.

The sulfamide functional group has previously found use in the design of other pharmacological agents in a wide variety of applications.[71] Aldrich *et al.*[72,73,74] have reported the use of sulfamide as an isosteric replacement for phosphate in a search for anti-mycobacterial agents. Previous work has led us to believe that a sulfamide may be a good isostere for the replacement of the phosphate of DPA, for example as in mimics of DPA such as compound **1.62**.



1.62

1.4 Design dTMP analogues as inhibitors of dTMPK

Another goal of this project was to synthesise sulfamides of thymidine as potential inhibitors of thymidine monophosphate kinase (TMPK*mt*). The recently discovered enzyme *Mycobacterium tuberculosis* TMPK*mt* is indispensable for the growth and survival of *M. tuberculosis*, as it plays an essential role in DNA synthesis.[75] Therefore the enzyme TMPK*mt*, which is involved in the *de novo* and salvage pathways (see below), might be an attractive target for the design of novel anti-tuberculosis agents.

1.4.1 *De novo* and salvage pathways

Enzymes involved in pyrimidine biosynthesis have a vital role in cellular metabolism, as they provide nucleosides that are essential components of many biomolecules.[76] *De novo* and salvage are the two major pathways for pyrimidine nucleotide synthesis. Since the *de novo* synthesis requires more energy, cells use the salvage pathway to re-use nucleosides derived from waste nucleotides.[77] The *de novo* and salvage pathways are essential for all bacterial cells and differ among species.[78] A number of enzymes are involved in the pyrimidine salvage pathway, including deoxycytidine triphosphate (dCTP) deaminase, deoxyuridine triphosphatase (dUTPase), thymidylate synthase, dTMP kinase, and several other enzymes (**Figure 1.13**).

Nucleoside monophosphate kinases are key enzymes for the synthesis of nucleoside triphosphates, which are the precursors of a number of major biological molecules such as DNA, RNA, and phospholipids.

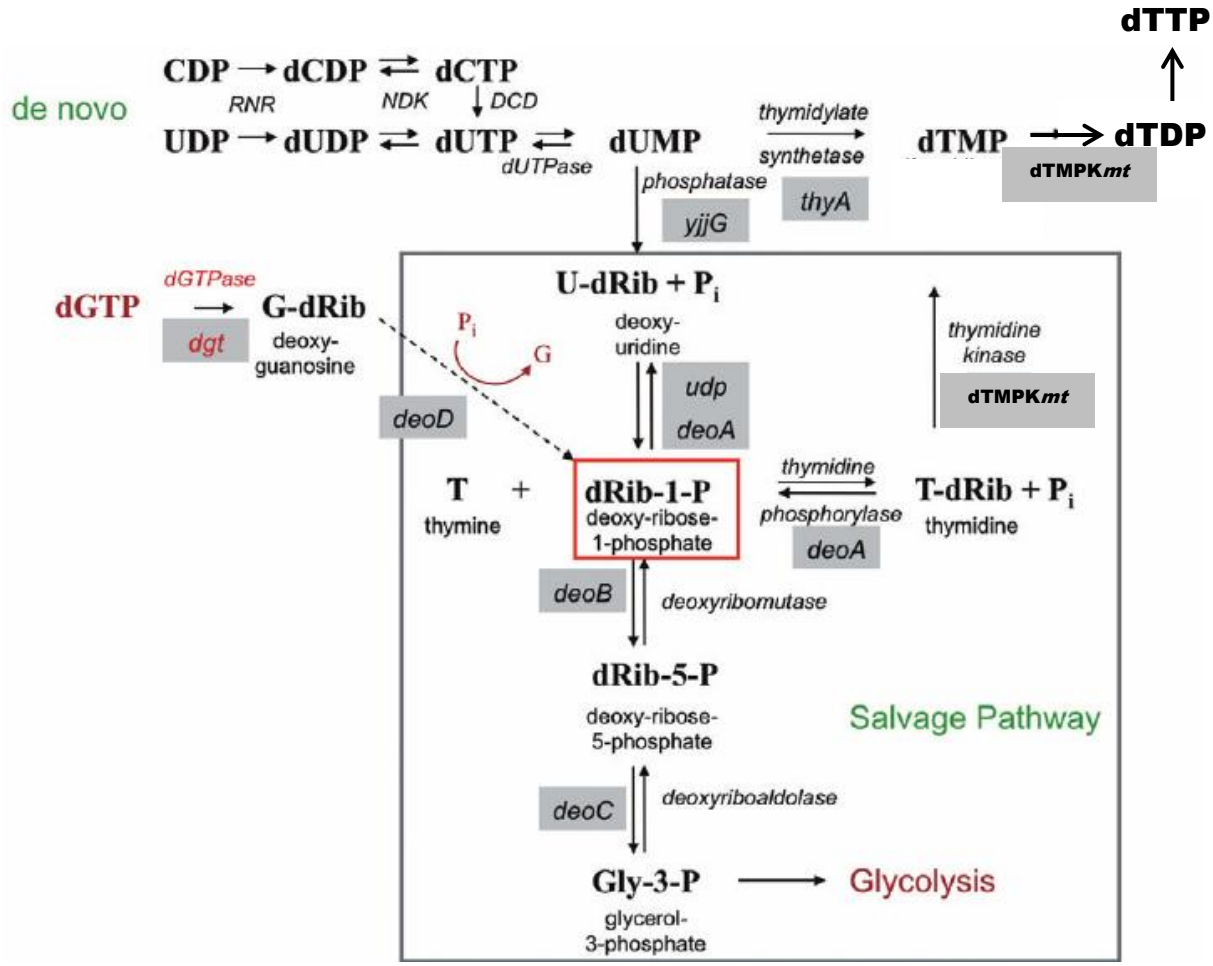


Figure 1.13 *De novo* and salvage pathways for nucleotide synthesis. Adapted from Zaritsky *et al.*[84]

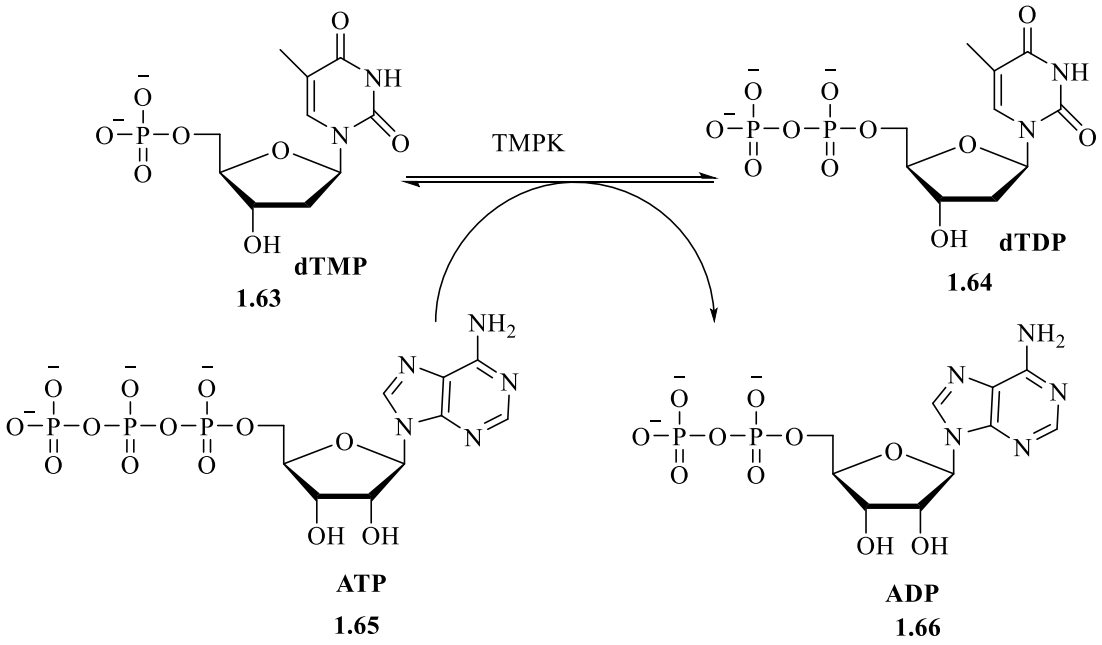


Figure 1.14 Biosynthesis of dTDP from dTMP

TMPK*mt* is inhibited by azidothymidine monophosphate (AZT-MP), but the AZT-MP does not inhibit any mammalian TMPKs, which suggests that inhibitors of TMPK*mt* could selectively block bacterial DNA synthesis.[85,86] Therefore, the enzyme TMPK*mt* is an attractive target for the design of novel anti-tuberculosis agents.

1.4.3 The dTMP binding site of TMPK*mt*

The X-ray structure of *TMPKmt* reveals the following main binding interactions between dTMP and the enzyme active site (**Figure 1.15**).

(i) The active site contains Mg^{2+}, H_2O, and an Arg95 (R95) residue. Non-bridging oxygens of the phosphate moiety form H-bond with Y39, P36 and an ionic interaction with R95 and Mg^{2+}.

(ii) A stacking interaction between the pyrimidine ring of thymine and Phe70 (F70).

(iii) H-bonds between the carbonyl (4-O) and amino groups (3-N) of dTMP and the side chains of residues Arg74 (R74) and Asn100 (N100) respectively.

(iv) Another H-bond is formed between the 3'-OH of the deoxyribose and the carboxylate of Asp9 (D9), which also makes polar contacts with the water molecule (w1009) involved in Mg^{2+} coordination and two other contacts with Asp9.

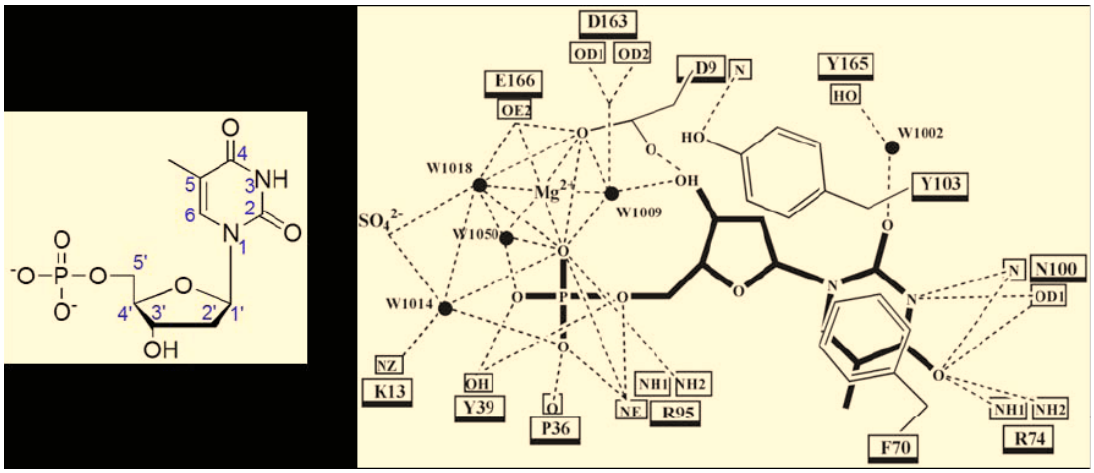


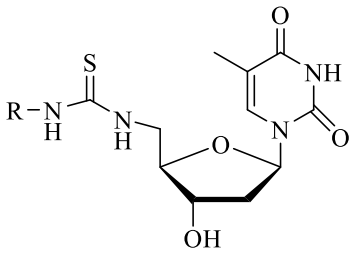
Figure 1.15 Schematic diagram of the dTMP binding site of TMPK*mt.* Adapted from Calenbergh *et al.* [87]

These enzyme-substrate interactions suggest that substrate-based competitive inhibitors could be designed by replacement of the 5'-phosphoryl group with a suitable isostere.

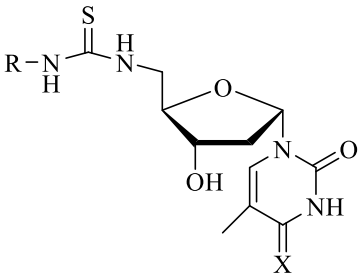
1.4.4 Previous work on the design and synthesis of inhibitors of TMPK*mt*

Various approaches have been reported for the modification of either the sugar or base moiety of thymidine in order to synthesise TMPK*mt* inhibitors; the positions modified so far include 2', 3', 5' and 5. Munier-Lehmann *et al.*[85,86] reported that AZT-MP behaves as an inhibitor of TMPK*mt* with a K_i value of 10 µM, whereas AZT has a K_i of 28 µM. Thymidine and other 5'-modified analogues (5'-azido or 5'-amino-5'-deoxy thymidine) were also discovered to be competitive inhibitors of TMPK*mt*, with affinities in the same range as the natural substrate dTMP (K_m= 4.5 µM).[86]

Calenbergh *et al.*[80] synthesized 5'-thiourea substituted thymidine derivatives **1.67-1.69**, and evaluated their inhibition of TMPK*mt*. The synthesis of thiourea analogue **1.67** is shown in **Figure 1.16** and **Scheme 1.8**.

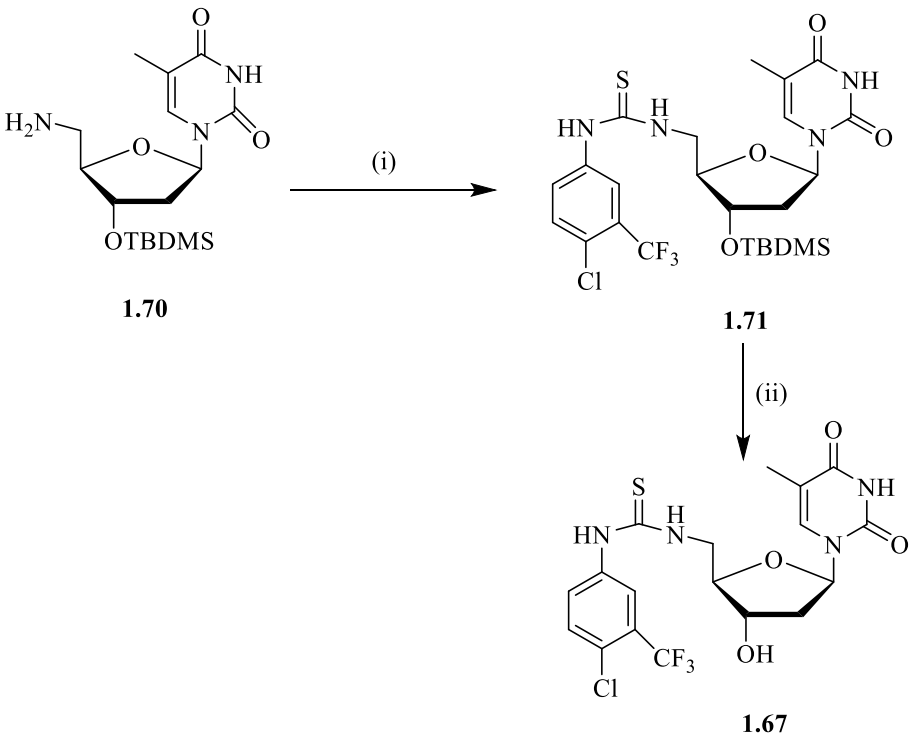


1.67 R = 3-CF_3-4-Cl-Phenylthiourea



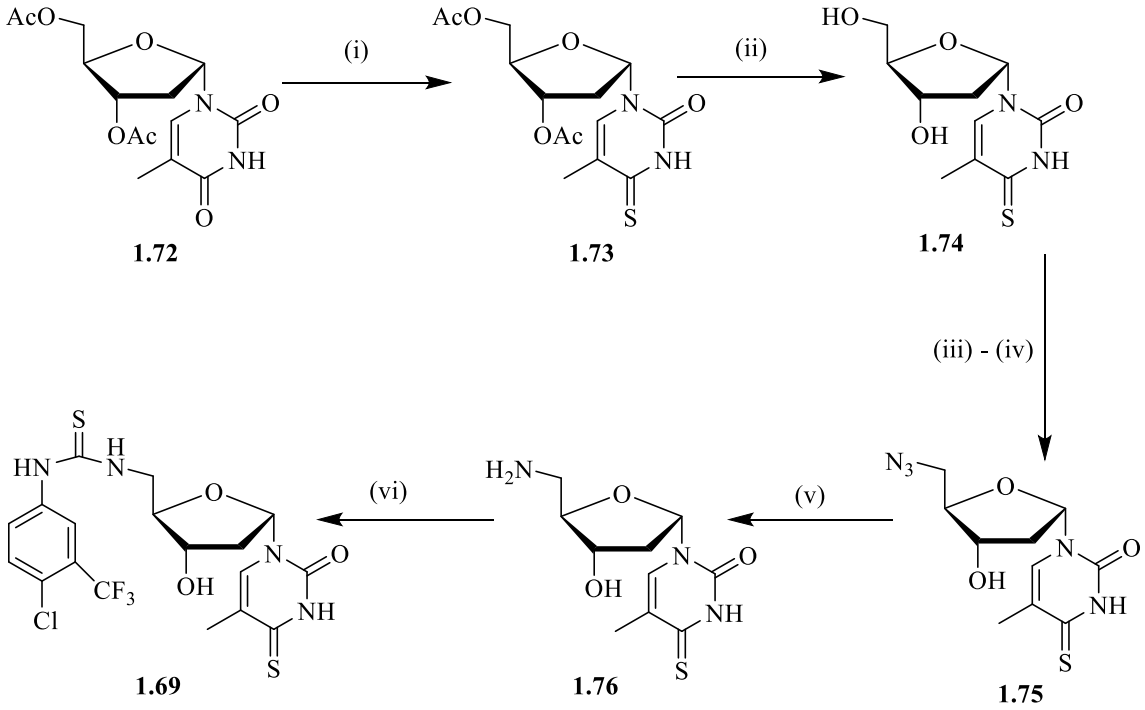
1.68 R = 3-CF_3-4-Cl-Phenylthiourea, X = O
1.69 R = 3-CF_3-4-Cl-Phenylthiourea, X = S

Figure 1.16 Analogues of dTMP reported by Calenbergh *et al.*[80]



Scheme 1.8 Synthetic production of 5'-thiourea substituted thymidine derivatives **1.67** reported by Calenbergh *et al.*[80]; (i) 4-chloro-3-(trifluoromethyl)phenyl isothiocyanate, DMF, 0 °C to rt; (ii) 1 M TBAF in THF, THF, rt.

For the synthesis of compound **1.67**, amine **1.70** was first coupled with 4-chloro-3-(trifluoromethyl)phenyl isothiocyanate, and the TBDMS group was subsequently removed using TBAF in THF. The α-anomer **1.68** was synthesized by the same route as the β-anomer.



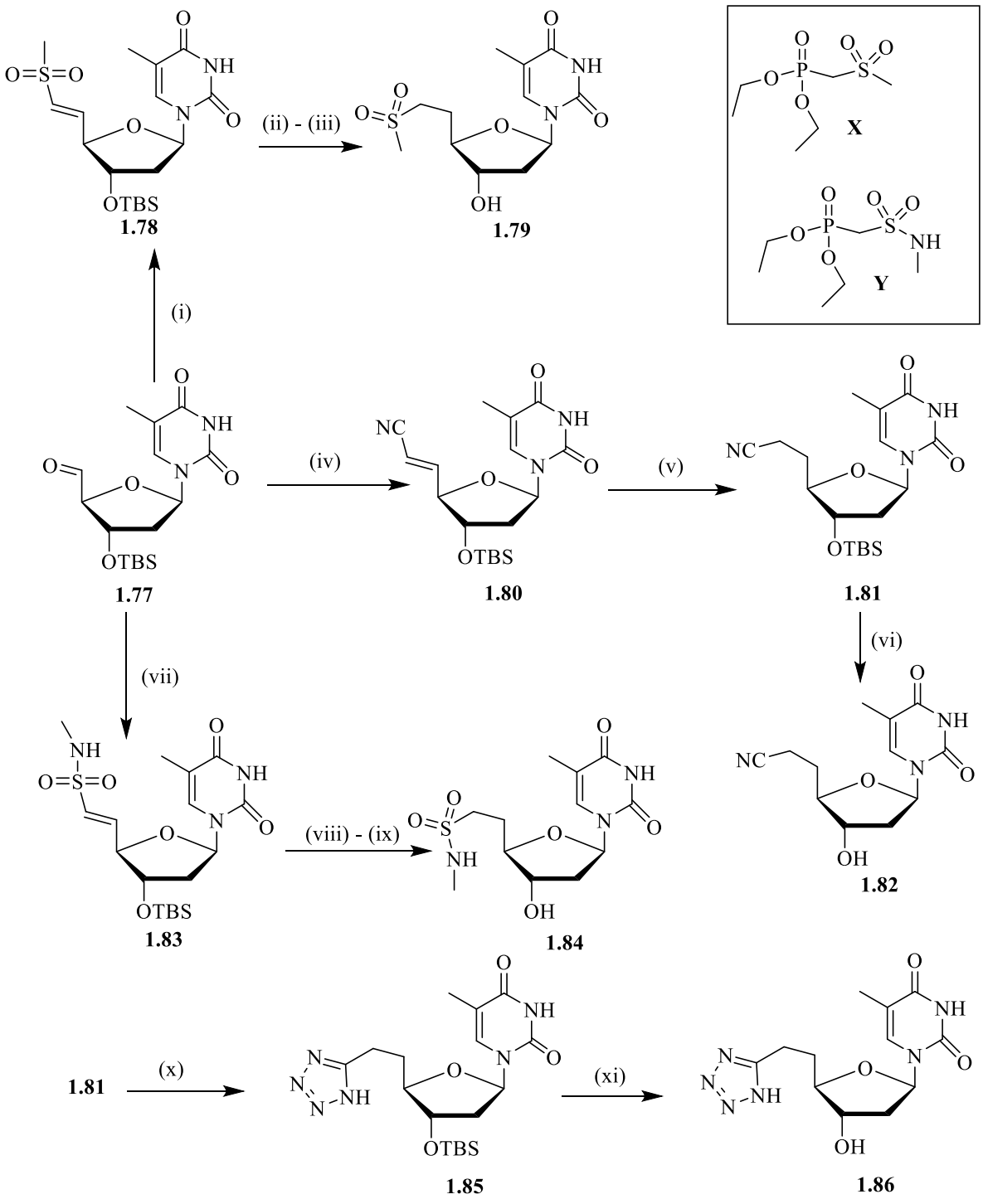
Scheme 1.9 Synthetic production of 5'-thiourea substituted thymidine derivative **1.69** reported by Calenbergh *et al.*[80]; (i) Lawesson's reagent, 1,4-dioxane, reflux; (ii) 7N NH_3 in MeOH, rt; (iii) MsCl, py, -78 °C to 0 °C; (iv) NaN_3, DMF, 60 °C; (v) PPh_3, H_2O, THF, rt; (vi) 4-chloro-3-(trifluoromethyl)phenyl isothiocyanate, DMF, 0 °C to rt.

For the preparation of 4-thio derivative **1.69**, 5'-*O*-acetylated derivative **1.72** was first treated with Lawesson's reagent to give 4-thio pyrimidine **1.73**. Subsequent hydrolysis of the acetate protecting groups afforded **1.74**. The primary hydroxyl was selectively mesylated, followed by azide substitution to yield azido derivative **1.75**, which was then reduced under Staudinger reaction conditions. The coupling of amine **1.76** with 4-chloro-3-(trifluoromethyl)phenyl isothiocyanate affored 4-thio-AZT **1.69** (**Scheme 1.9**).

The inhibitory activity of thiourea derivatives **1.67-1.69** were evaluated against TMPK*mt*. The 5'-phenylthiourea-substituted β-thymidine derivative **1.67** showed moderate inhibitory activity, with a K_i of 14.5 μM, however, the α-anomer **1.68** was 24-fold more active (K_i of 0.6 μM) than the β-anomer. The replacement of oxygen at

position 4 with sulphur (**1.69**) increased the activity by a factor of 3 (K_i 0.17 μM), the synthesis of compound **1.69** analogue is shown in **Scheme 1.9**.

Recently, the following series of 5'-modified thymidine derivatives **1.79**, **1.82**, **1.84** and **1.86** were prepared as shown in **Scheme 1.10** by Calenbergh *et al.*[81]

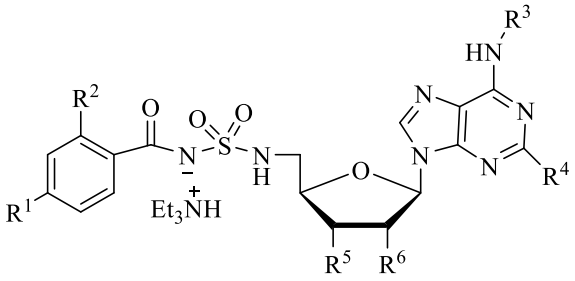


Scheme 1.10 Synthesis of dTMP analogues reported by Calenbergh *et al.*[81]; (i) **X**, *n*-BuLi, THF, -78 °C to rt; (ii) H_2, Pd/C, MeOH, rt; (iii) TBAF, THF, 40 °C; (iv) $ClPPh_3CH_2CN$, *n*-BuLi, THF, 0 °C to rt; (v) py-MeOH (3:1), $NaBH_4$, 120 °C; (vi) TBAF, THF, rt; (vii) **Y**, *n*-BuLi, THF, -78 °C to rt; (viii) MeOH-THF (5:1), $NiCl_2$, $NaBH_4$, 0 °C; (ix) TBAF, THF, 40 °C; (x) $TMSN_3$, Bu_2SnO, toluene, 110 °C; (xi) TBAF, THF, rt.

To synthesise 5'-modified derivatives, the 5'-OH of 3'-silylated thymidine was oxidized using Dess-Martin periodinane, and the resulting aldehyde **1.77** was treated with Wittig-Horner reagents to give compounds **1.78**, **1.80** and **1.83**. Methylsulfone **1.79** was obtained by catalytic hydrogenation followed by removal of the TBS group. The alkenes in **1.80** and **1.83** were reduced using $NaBH_4$ and $NaBH_4/NiCl_2$ respectively, and subsequent TBS deprotection using TBAF afforded **1.82** and **1.84**. A cycloaddition of nitrile **1.81** and $TMSN_3$ using dibutyltin oxide yielded tetrazole **1.85**, which was then desilylated using TBAF to afford the target tetrazole **1.86**.

The inhibitory activity of compounds **1.79**, **1.82**, **1.84** and **1.86** against TMPK*mt* was assessed by a spectrophotometric binding assay. Compounds **1.82** and **1.86** showed moderate activities, with K_is of 48 µM and 70 µM respectively. However, the other compounds were less active.

These previous studies have demonstrated that the suitable isosteric replacement of phosphate can produce sub-micromolar inhibitors of TMPK*mt*. There are only a few reports on the use of sulfamides as a phosphate isostere in the search for anti-mycobacterial agents. For example, Aldrich et al. [72,73,74] recently reported the synthesis of salicyl sulfamoyl adenosine **1.87** and derivatives, which displayed promising inhibitory activity with MICs ranging from 0.19-6.25 µg/mL against *M. tuberculosis*. These adenosine analogues disturb siderophore biosynthesis by inhibition of an adenylate-forming enzyme MbtA, which is involved in biosynthesis of the mycobactins.



1.87

Based on these previous reports, we believed that sulfamide could be a good isostere for the replacement of the labile phosphate of dTMP.

1.5 Project objectives

The objective of this research project was to synthesise a series of sulfamide analogues of DPA and dTMP, where sulfamide is an isostere of the labile phosphate group, for use in anti-TB drug development.

This thesis describes the synthesis of sulfamides as analogues of DPA and dTMP, and evaluation of their anti-mycobacterial activity against *M. smegmatis* using an Alamar Blue assay. An additional Chapter includes the expeditious discovery and subsequent development of a highly practical new method for the reduction of organic azides to primary amines.

Chapter 2 describes the synthesis of sulfamides as analogues of DPA, and evaluation of their anti-mycobacterial activity. The effect of the alkyl chain length and the effect of insertion of oxygen atoms into the linear alkyl chain were investigated.

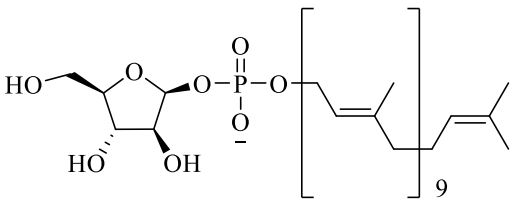
Chapter 3 describes docking studies and the synthesis of sulfamide derivatives of thymidine as dTMP analogues. Investigations of the anti-mycobacterial activity of sulfamide analogues of dTMP are also reported.

Chapter 4 details the discovery and development of a new method for the chemoselective reduction of primary amines from azides.

Chapter 2 The synthesis of DPA analogues as anti-TB agents.

2.1 Introduction

The mycobacterial cell wall contains two polysaccharides, lipoarabinomanan (LAM) and arabinogalactan (AG), which are crucial to mycobacterial growth and survival.[88] Biosynthesis of the mycobacterial cell wall requires several different sugar-processing enzymes. Glycosyltransferases, for example galactofuranosyl transferases and arabinofuranosyltransferases (AraT's), are responsible for the assembly of the glycans.[30] AraT's are responsible for assembling the arabinan portion of the two oligosaccharides, and use decaprenyl phosphoarabinose DPA as the donor of the arabinofuranose residues.[13, 89] Oligosaccharides containing arabinofuranose residues are not found in mammals, and the enzymes involved in the biosynthesis of these glycans are therefore excellent targets for drug development.[22, 90] Therefore, analogues of DPA would be expected to block cell wall biosynthesis by inhibiting AraT's, which is particularly important for treating MDR-TB and XDR-TB.

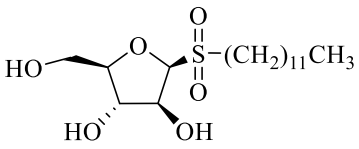


Decaprenolphosphoarabinose (DPA)

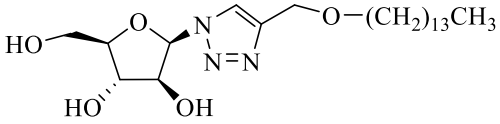
Ethambutol, a widely used anti-mycobacterial agent, was found to inhibit arabinofuranosyltransferase activity in the DPA assay described by Lee et al.[67] to a residual activity of 40% at 50 μg/mL, coincubation with a variety of enzymic cofactors was not affected the residual activity. The results suggests that metabolically stable analogues of DPA are a substrate for more than one AraT, and

would therefore be expected to block a number of biosynthetic steps and, in turn, be expected to compromise mycobacterial viability. In order to design mimics of DPA, replacement of the labile and highly polar glycosyl phosphate with a suitable isostere[59], and an alkyl chain is required to mimic the large hydrophobic side chain.

As mentioned in the previous chapter, analogues of DPA have previously been synthesized by the Fairbanks group[63,64] and several others.[25-26, 42, 65, 91] Amongst the synthetic analogues synthesised by Fairbanks *et al.*, compounds **1.53e** and **1.45d** displayed the most promising inhibitory activity against *M. bovis*; exhibiting minimum inhibitory concentration (MICs) of 62 µg/mL and 31 µg/mL respectively. These values should be compared with those of currently used anti-TB drugs: the activity of compounds **1.53e** and **1.45d** is approximately one order of magnitude lower than the anti-TB drugs isoniazid (0.1 µg/mL) and ethambutol (4 µg/mL). It may appear, therefore, that a large increase in activity is required for this type of arabinofuranose derivative to become serious drug candidates.



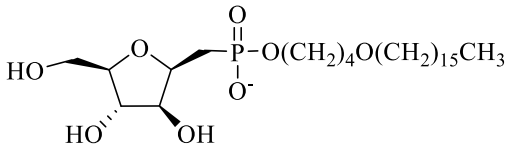
1.53e



1.45d

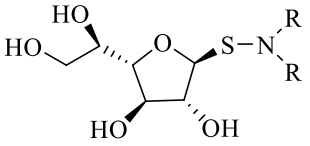
Previously, a series of C-phosphonate analogues of DPA had been synthesized by Lowary *et al.*[42] One of these C-phosphonates **1.25f** displayed promising inhibitory potency against *M. tuberculosis*, with a MIC of 3.13 µg/mL. Based on this success, a series of sulfone and phosphonic acid analogues bearing different length hydrophobic

chains were synthesized. However, screening of these compounds revealed that in fact none was as potent as **1.25f**.[61]

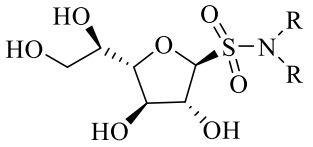


1.25f

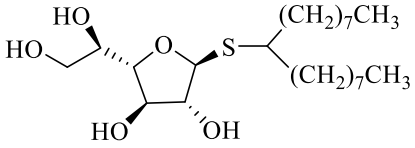
However, such increases in activity have already been demonstrated by Von Itzstein *et al*.[65] for galactofuranose compounds; a series of galactofuranosyl *N*,*N*-dialkylated sulfonamides **2.1** and sulfonamides **2.2** were synthesized and number of these displayed strong anti-mycobacterial activity with MIC values below 5 μg/mL against *M. smegmatis*.[65]. Notably the shorter alkyl chain *N*,*N*-dihexyl sulfonamides had lower potency than *N*,*N*-dioctyl and *N*,*N*-didecyl derivatives; this simple structural variation caused more than a 64-fold decrease in the MIC value. In addition, the *N*,*N*-dioctyl sulfonamide had 2 fold higher activity than the corresponding sulfenamide.[65] Furthermore, Von Itzstein *et al*.[70] also synthesized galactofuranosyl alkyl thioglycosides as possible analogues of uridine diphosphate galactofuranose (UDP-Gal*f*), which use as the donor of the galactan biosynthesis. The 9-heptadecyl thioglycoside **1.59c** and sulfone **1.61c** displayed significant inhibitory potency against *M. smegmatis* with the MIC of 1 μg/mL and 2 μg/mL respectively, which is comparable that of *N*,*N*-dioctyl sulfonamide and *N*,*N*-dioctyl sulfenamide.



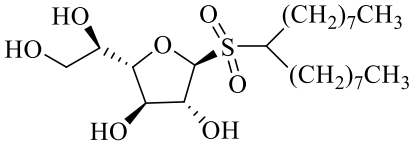
2.1



2.2

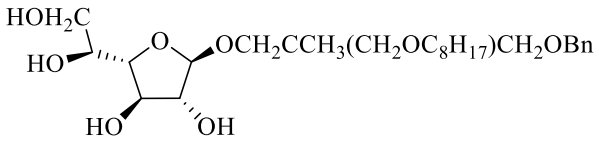


1.59c



1.61c

More recently, Legentil *et al.*[66] synthesized a series of 1,2-*trans* alkyl galactofuranosides; from these a mixed alkyl/aryl β-D-galactofuranoside **2.8** had the best inhibitiory activity (MIC 90 μM) against *M. smegmatis.*



2.3

Aldrich *et al.*[72, 74] have reported the use of sulfamide as an isosteric replacement for phosphate in a search for anti-mycobacterial agents. The sulfamide functional group has previously found use in the design of many other pharmacological agents in a wide variety of applications.[71] Previous work has led us to believe that a sulfamide-based unit may be a good isostere for the replacement of the phosphate part of DPA. In addition, Lowary *et al.*[42], Fairbanks *et al.*[63] and von Itzstein *et al.*[65] have demonstrated that the hydrophobicity of the side chain is essential for biological activity.

Based on an assessment of these previous studies, the polarity, the availability of heteroatoms for hydrogen bonding and the tetrahedral nature of the central sulfur atom reinforced the idea that glycosyl sulfamides with varying hydrophobic side chains may be useful mimics of DPA. In this project a four series of β-arabinofuranosyl sulfamides, namely: mono-substituted, di-substituted, oxygenated and prenylated series, were selected as potential inhibitors (**Figure 2.1**).

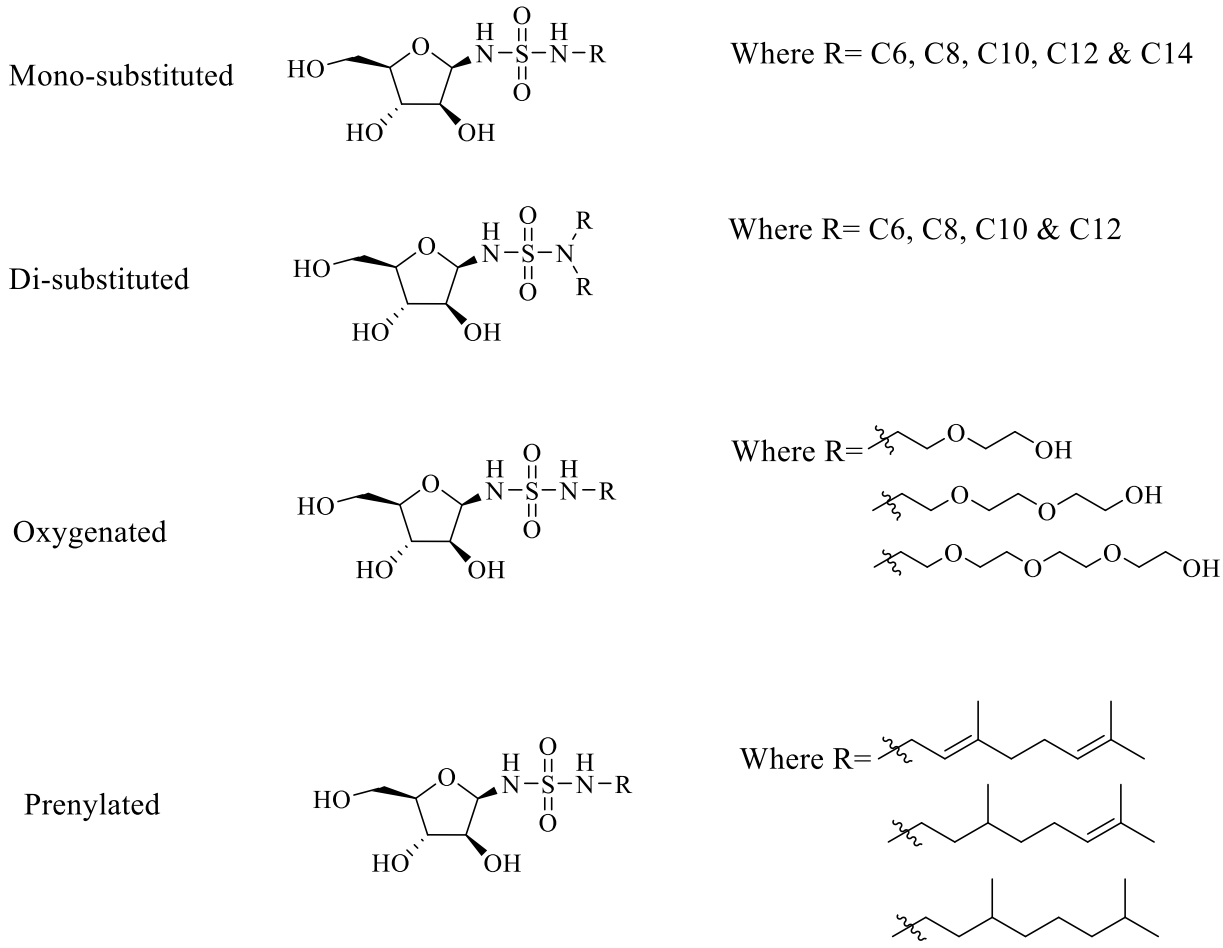
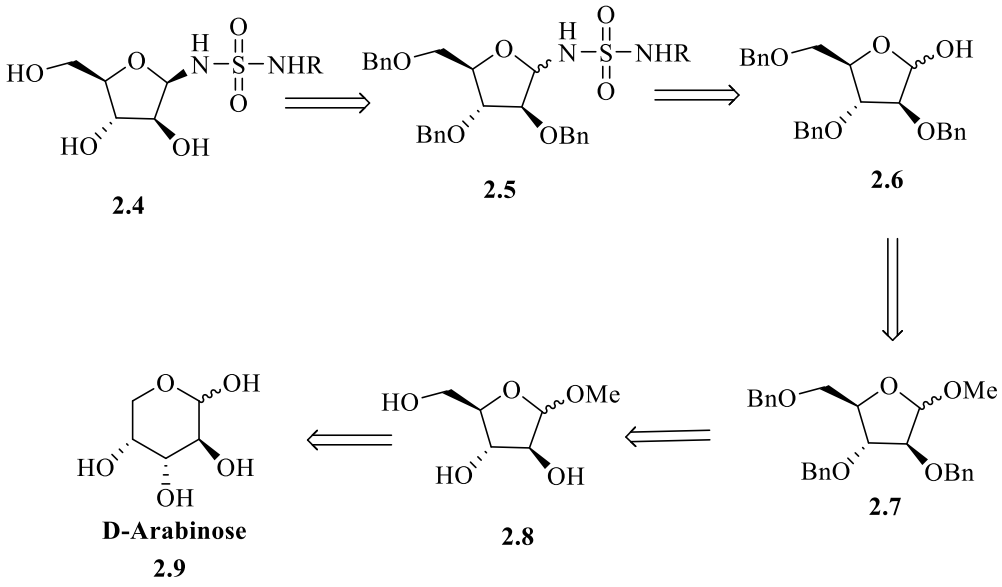


Figure 2.1 *N*-Glycosyl sulfamide targets as DPA analogues.

2.2 The synthesis of glycosyl sulfamides and anti-mycobacterial activities

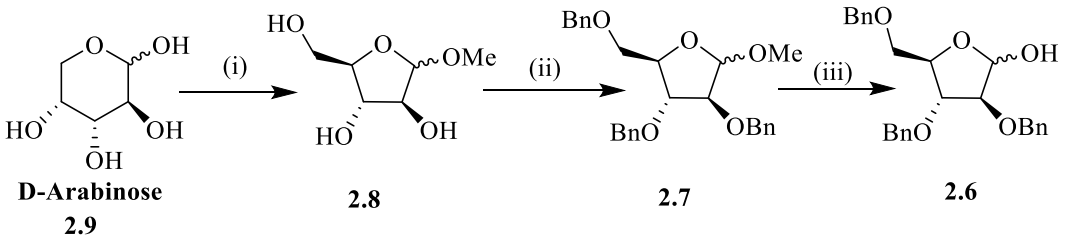
2.2.1 Retrosynthetic analysis

A retrosynthetic analysis of glycosyl sulfamides **2.4** is shown in **Scheme 2.1**. Commercially available D-arabinose **2.9** exists as an equilibrium mixture of pyranose, furanose, and acyclic forms in solution, with the pyranose form predominating. It was envisaged that D-arabinose could be converted to methyl furanoside **2.7**, and the C-2, C-3, and C-5 alcohols could then be protected with benzyl groups. Donor **2.6,** readily synthesised from **2.7**, could then be glycosylated with sulfamide acceptors. The final product could be obtained by de-protection of the benzyl groups followed by isolation of β-anomer of the furanoside using HPLC.



Scheme 2.1 Retrosynthetic analysis of *N*-glycosyl arabino furansosyl sulfamides

2.2.2 Synthesis of the arabinose donor 2.6



Scheme 2.2 (i) AcCl, MeOH, 3 h; (ii) NaH, BnBr, DMF, 16 h, 54 %; (iii) AcOH:H_2O (4:1, v/v), 115 °C, 24 h, 64 %.

The tri-benzylated D-arabinofuranoside glycosyl donor was synthesized following methods published by Vanderklein *et al.*,[92] as shown in **Scheme 2.2**. D-Arabinose was suspended in methanol and acid-catalysed (AcCl, 3 equiv.) Fischer glycosylation was carried out to afford the kinetic product, furanoside as a mixture of anomers **2.8** (**Figure 2.2**).

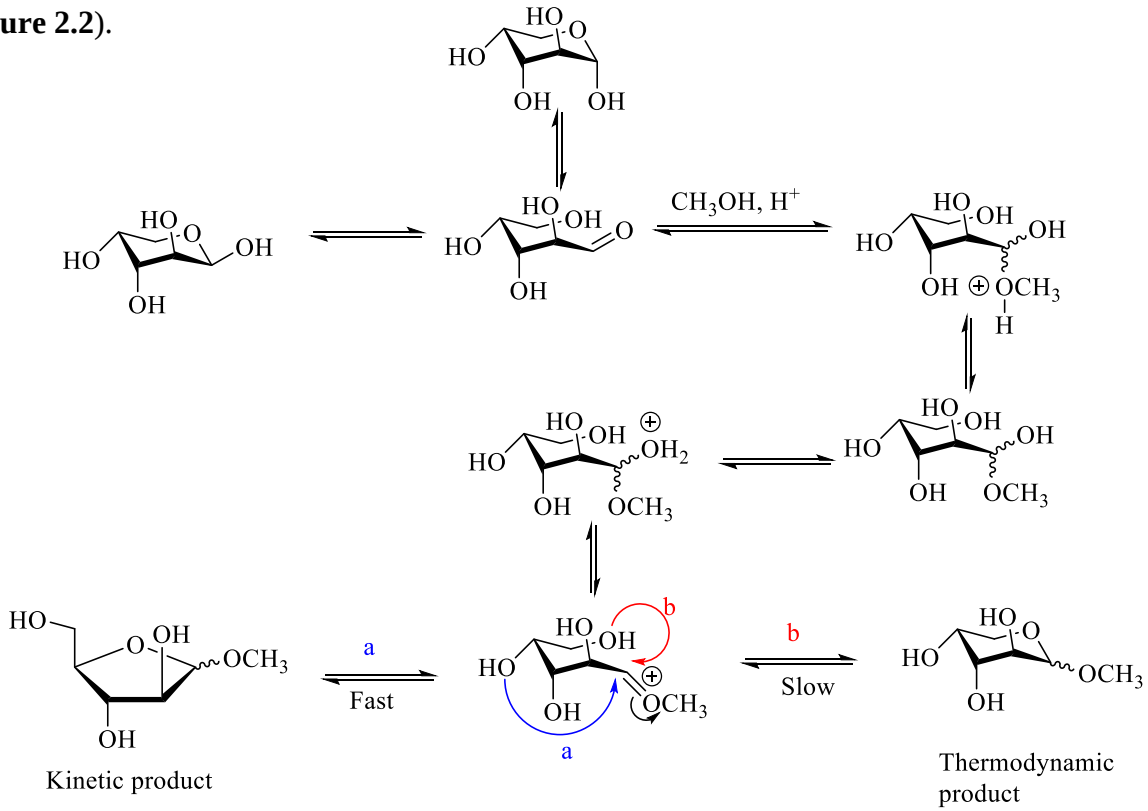


Figure 2.2 Mechanism of Fischer glycosylation of D-arabinose

The reaction was quenched after three hours to avoid the formation of the undesired pyranose form, which is the thermodynamic product. Methyl α,β-D-arabinofuranoside **2.8** was then benzylated with sodium hydride and benzyl bromide in DMF to afford tri-benzylated derivative **2.7**, which was then hydrolysed by treatment with 80 % acetic acid to give the target glycosyl donor **2.6**. Donor **2.6** was confirmed to be in the furanose form by X-ray crystallography (**Figure 2.3**).

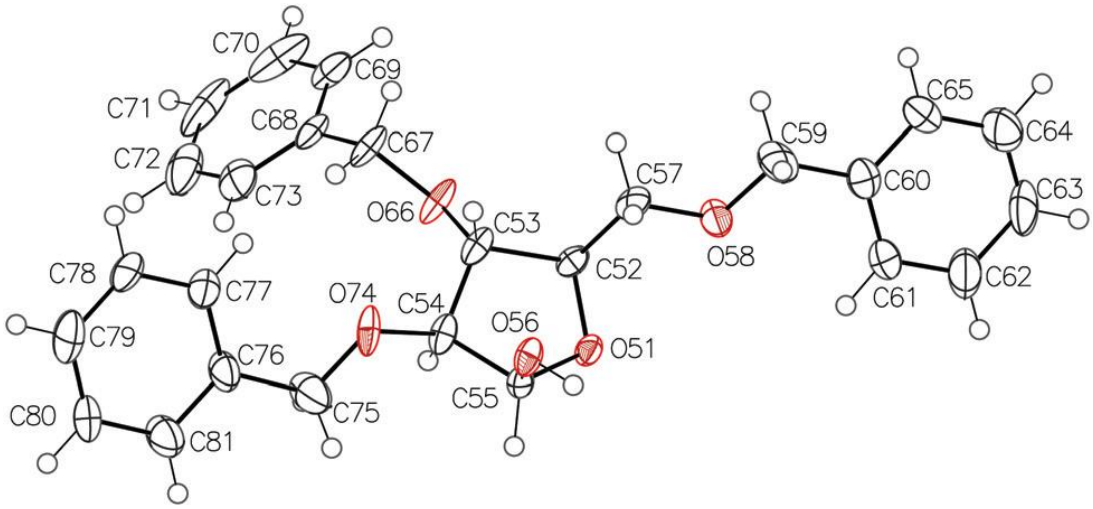
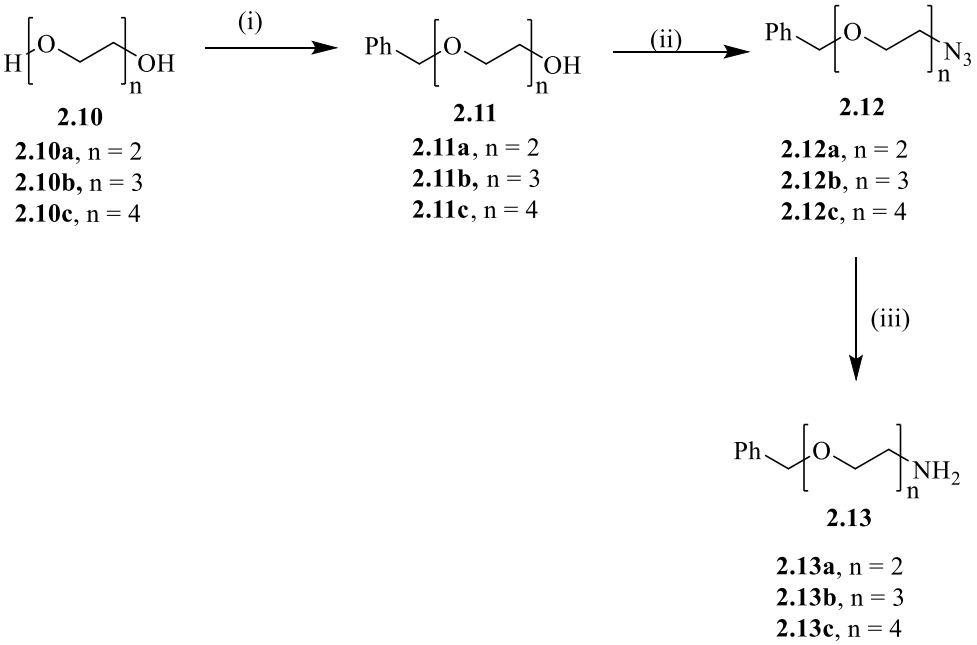


Figure 2.3 X-Ray structure of arabinofuranose hemiacetal **2.6**

2.2.3 Synthesis of sulfamide acceptors

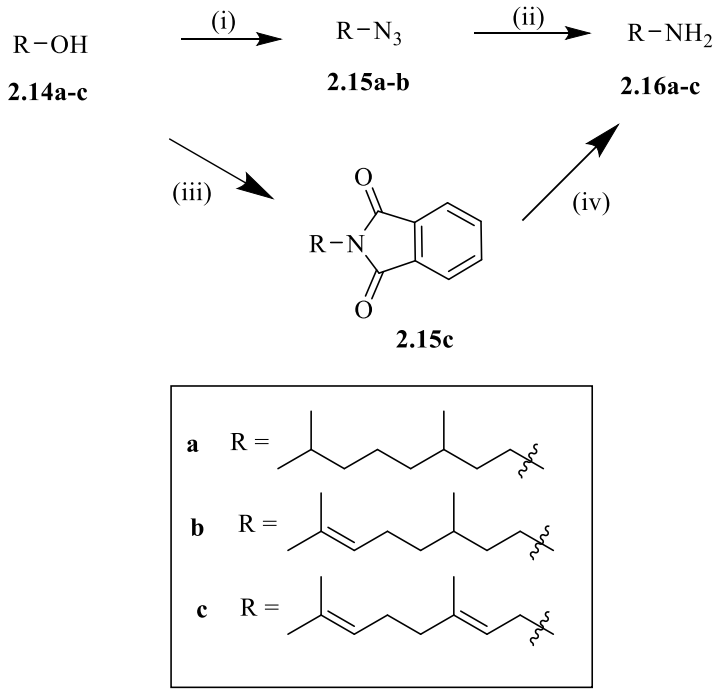
A series of polyethylene glycol (PEG) derivatives were synthesised (**Scheme 2.3**) to systematically investigate if there was any effect of incorporating more polar groups into the side chains of the DPA mimics. One of the hydroxyl groups of triethyleneglycol **2.10b** was protected as a benzyl ether by using NaH (0.5 equiv.) and BnBr (0.5 equiv.) to afford the monobenzylated derivative as the major product, together with a small amount of the dibenzylated compound. Purification by flash chromatography afforded the pure mono benzylated compound **2.11b**. Similar

monobenzylation of di- and tetra-ethyleneglycol (**2.11a** and **2.11c**) was performed by a previous Postdoc in the Fairbanks group (Andrew Watson). The free hydroxyl groups of the mono-benzylated di-, tri- and tetra-ethyleneglycol derivatives **2.11a-c** were converted into a good leaving group (mesylate) by treatment with methanesulfonyl chloride (1.5 equiv.) in the presence of Et_3N (1.5 equiv.). The mesylates were then directly treated with sodium azide to afford azides **2.12a-c**, which were then reduced to amines **2.13a-c** by reaction with PPh_3 and water via the Staudinger reaction.



Scheme 2.3 (i) NaH, BnBr, DMF, 0 °C to rt, 16 h, **2.11b** – 36 %; (ii) MsCl, Et_3N, DCM, 0 °C, 2 h; NaN_3, DMF, 60 °C, 16 h, **2.12a** – 94 %: **2.12b** – 97 %: **2.12c** – 91 %; (iii) PPh_3, H_2O, THF, rt, 16 h, **2.13a** – 71 %: **2.13b** – 80 %: **2.13c** – 67 %.

In order to better mimic the polyprenol chain of DPA, a series of glycosyl sulfamides bearing methyl branched side chains were synthesized (**Scheme 2.4**). Amine terminated methyl branch alkyl chains were made from commercially available alcohols **2.14a-c,** by an analogous sequence of mesylation and azide displacement to yield azides **2.15a-b**, and then Staudinger reduction to yield amines **2.16a-b.**



Scheme 2.4 (i) MsCl, Et_3N, DCM, 0 °C, 2 h; NaN_3, DMF, 60 °C, 16 h, **2.15a** – 75 %: **2.15b** – 56 %; (ii) PPh_3, H_2O, THF, rt, 16 h, **2.16a** – 63 %: **2.16b** – 71 %; (iii) MsCl, Et_3N, DCM, 0 °C, 2 h; potassium ththalimide, 70 °C, 16 h, **2.15c** – 60 %; (iv) $N_2H_4.H_2O$, reflux, 16 h, **2.16c** – 43 %.

However an attempt to convert geraniol **2.14c** to the corresponding azide by this method as mentioned above was unsuccessful, as allylic azides undergo a rapid [3,3] sigmatropic rearrangement (**Figure 2.4**), resulting in a dynamic equilibrium of several isomers. An alternative route was devised using a Gabriel synthesis, wherein the hydroxyl group of geraniol was first converted to a mesylate, and this was then treated with potassium phthalimide to give compound **2.15c**, which was finally converted to geranyl-amine **2.16c** by treatment with hydrazine hydrate.

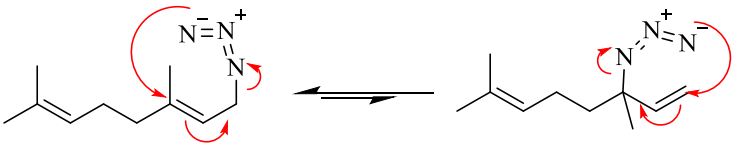
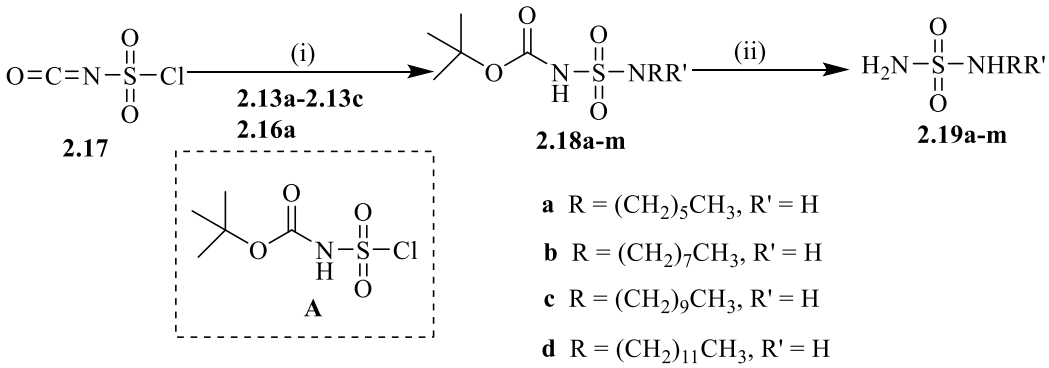


Figure 2.4 Allylic azide rearrangement

It is difficult to achieve chemoselective removal of the benzyl ethers under standard condition using catalytic hydrogenation in the presence of the side chain alkenes. However, the target citronellyl and geranyl sulfamides derivatives could be achieved using suitable protecting groups, such as benzoyl or acetate for the synthesis of arabinose donor. As described later in this chapter, all the target deprotected sulfamide analogues underwent isomerization from the desired furanose to thermodynamically more stable pyranose form. Thus, it will be insignificant in synthesizing the undesired pyranose form of citronellyl and geranyl sulfamides using a different route. Therefore, only glycosyl sulfamides that possessed a fully saturated side chain were synthesised.

A series of sulfamide acceptors bearing linear alkyl side chains of varying length were synthesized (**Scheme 2.5**) by the treatment of a variety of amines with different alkyl chains **2.13a-c** and **2.16a** using commercially available chlorosulfonyl isocyanate (1.0 equiv.) **2.17**. In the first step of this process, a sulfonyl chloride intermediate **A** is synthesized by using t-BuOH and chlorosufonyl isocyanate, which is then directly reacted with the primary amines incorporating different side chains to produce the corresponding Boc-protected sulfamides **2.18j-m.** Likewise, the mono- and di-substituted Boc-protected sulfamides **2.18a-i** were synthesised by a previous postdoc in the Fairbanks group (Andrew Watson) using primary and secondary amines respectively. Finally, in all cases the Boc protecting group was removed by treatment with trifluoroacetic acid (5.0 equiv.) to give the desired sulfamides **2.19a-m** in excellent yields (60-90%).



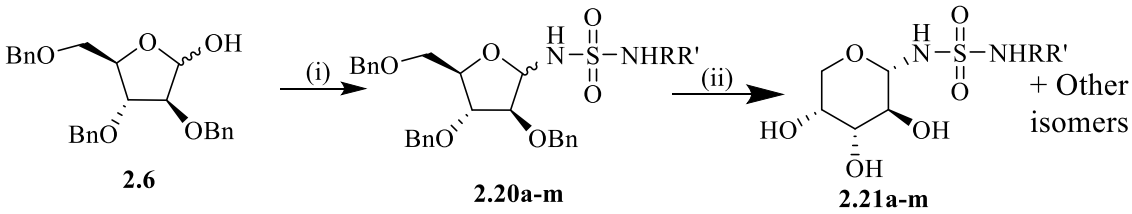
a R = $(CH_2)_5CH_3$, R' = H
b R = $(CH_2)_7CH_3$, R' = H
c R = $(CH_2)_9CH_3$, R' = H
d R = $(CH_2)_{11}CH_3$, R' = H
e R = $(CH_2)_{13}CH_3$, R' = H
f R = R' = $(CH_2)_5CH_3$
g R = R' = $(CH_2)_7CH_3$
h R = R' = $(CH_2)_9CH_3$
i R = R' = $(CH_2)_{11}CH_3$
j R = $(CH_2)_2CH(CH_3)(CH_2)_3CH(CH_3)_2$, R' = H
k R = $(CH_2)_2O(CH_2)_2OBn$, R' = H
l R = $(CH_2CH_2O)_2(CH_2)_2OBn$, R' = H
m R = $(CH_2CH_2O)_3(CH_2)_2OBn$, R' = H

Scheme 2.5 (i) t-BuOH, 2.17, DCM, 0 °C, 30 minutes; RNH_2, Et_3N, DCM, 0 °C to rt, 16 h, **2.18j** – 73 %; **2.18k** – 93 %; **2.18l** – 39 %; **2.18m** – 91 %; (ii) TFA, DCM, rt, 16 h, **2.19a** – 86 %; **2.19b** – 69 %; **2.19c** – 76 %; **2.19d** – 68 %; **2.19e** – 75 %; **2.19f** – 92 %; **2.19g** – 76 %; **2.19h** – 66 %; **2.19i** – 78 %; **2.19j** – 98 %; **2.19k** – 88 %; **2.19l** – 76 %; **2.19m** – 65 %.

2.2.4 Synthesis of sulfamidoglycosides

A previous Postdoc in the Fairbanks group (Brendan Wilkinson) had performed extensive investigations into trying to improve the stereoselectivity of the sulfamidoglycosylation, which gave poor β-stereoselectivity under a variety of activation conditions. Therefore, sulfamidoglycosylation was performed using the standard condition[93] as mentioned below. Condensation of the furanose hemiacetal **2.6** and the various sulfamide acceptors **2.19a-m** in the presence of stoichiometric trimethylsilyl trifluoromethanesulfonate (TMSOTf) afforded the corresponding

glycosyl sulfamides **2.20a-m** as inseparable mixtures of anomers (α:β 1:1). Compounds **2.20a-m** were then deprotected by catalytic hydrogenation in the presence of 10% Pd on carbon in MeOH under an atmosphere of hydrogen, to yield a mixture of compounds (**Scheme 2.6**), which were partially separated by HPLC.



a R = $(CH_2)_5CH_3$, R' = H

b R = $(CH_2)_7CH_3$, R' = H

c R = $(CH_2)_9CH_3$, R' = H

d R = $(CH_2)_{11}CH_3$, R' = H

e R = $(CH_2)_{13}CH_3$, R' = H

f R = R' = $(CH_2)_5CH_3$

g R = R' = $(CH_2)_7CH_3$

h R = R' = $(CH_2)_9CH_3$

i R = R' = $(CH_2)_{11}CH_3$

j R = $(CH_2)_2CH(CH_3)(CH_2)_3CH(CH_3)_2$

k R = $(CH_2)_2O(CH_2)_2OH$

l R = $(CH_2CH_2O)_2(CH_2)_2OH$

m R = $(CH_2CH_2O)_3(CH_2)_2OH$

Scheme 2.6 (i) TMSOTf, RR'$NHSO_2NH_2$, DCM, 0 °C to rt, 16 h, **2.20a** – 52 %; **2.20b** – 54 %; **2.20c** – 77 %; **2.20d** – 71 %; **2.20e** – 54 %; **2.20f** – 78 %; **2.20g** – 68 %; **2.20h** – 59 %; **2.20i** – 47 %; **2.20j** – 80 %; **2.20k** – 74 %; **2.20l** – 83 %; **2.20m** – 62 %. (ii) Pd/C, H_2, MeOH, rt, 16 h, **2.21a** – 42%; **2.21b** – 36 %; **2.21c** – 45 %; **2.21d** – 40 %; **2.21e** – 47 %; **2.21f** - 41 % **2.21g** – 45 %; **2.21h** – 41%; **2.21i** – 39 %; **2.21j** – 43 %; **2.21k** – 46 %; **2.21l** – 42 %; **2.21m** – 46%.

The three components, labelled **A**, **B**, and **C** from the deprotection of compound **2.21c** were separated by RP-HPLC (**Figure 2.5**) using a Luna C18 semi-preparative column (Phenomenex); eluent:A (0.05% TFA in H_2O) and B MeCN; gradient: the sample was run at 1 $mLmin^{-1}$ with a gradient of 50-85% B and analysed by NMR. Structural analysis of the each purified component by HMBC was unclear, and so the structure of the major component **A** (**2.21c**) was confirmed by X-ray crystallography (**Figure 2.6**), which is only one example chosen to study the isomerization and determination of the structure by X-ray crystallography.

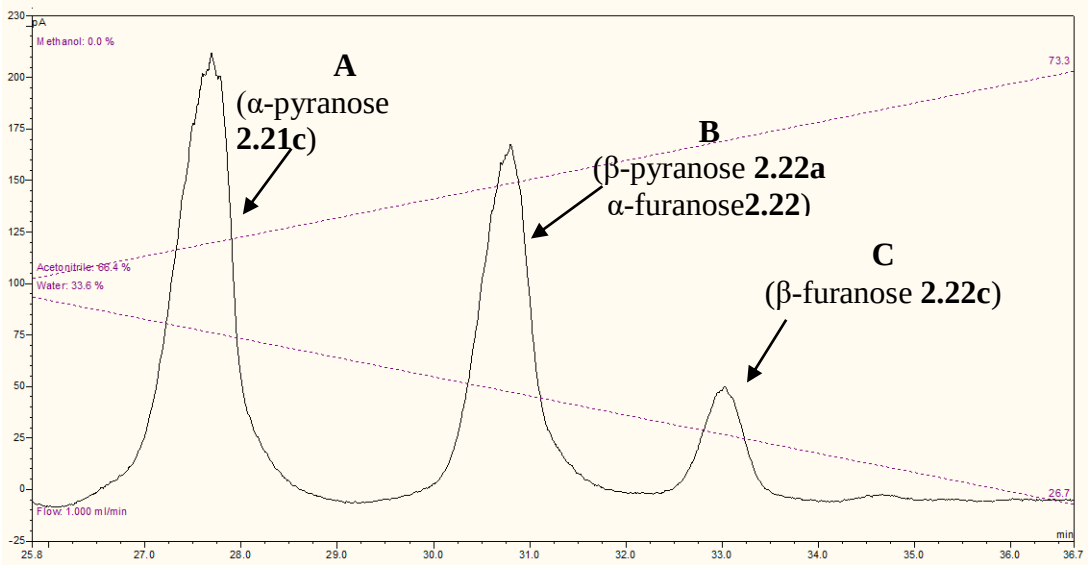


Figure 2.5 RP-HPLC trace of *N-(*decyl)-*N'*-(α,β-D-arabinopyranosyl)sulfamide **2.21c/2.22a** and *N-(*decyl)-*N'*-(α,β-D-arabinofuranosyl)sulfamides **2.22b/2.22c** equilibrated in water.

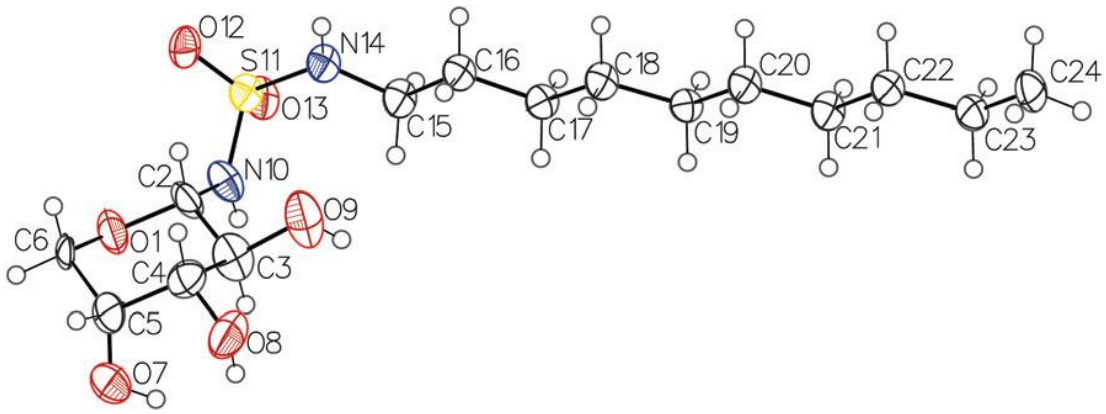


Figure 2.6 X-Ray structure of a α-pyranose sulfamide **2.21c.**

Unexpectedly, these crystallographic studies revealed **2.21c** to be the α-pyranose isomer, in a $^{1}C_{4}$ conformation. The other components of the mixture were then identified as the β-pyranose (**B**) and a mixture of the α- and β-furanose isomers (**C**).

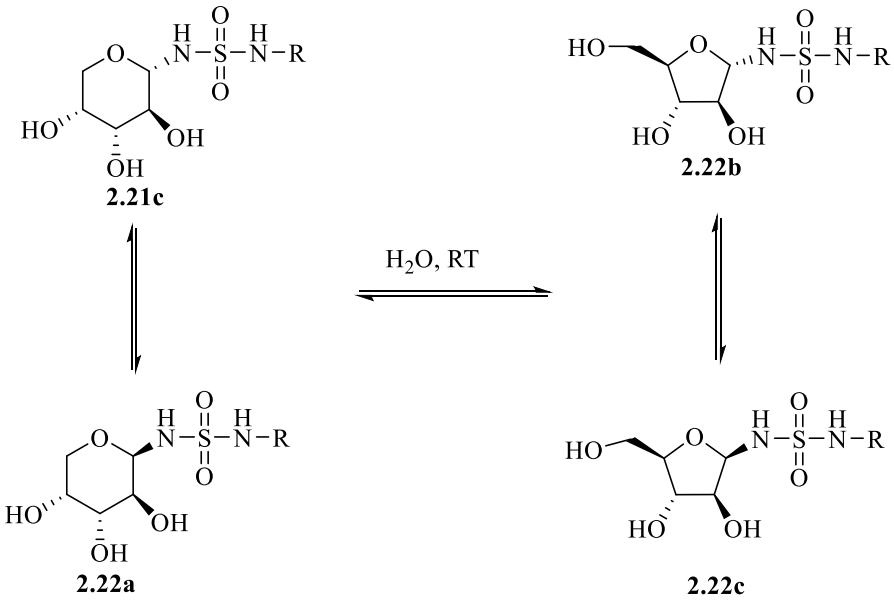


Figure 2.7 Equilibration of *N*-Glycosylsulfamides in aqueous solution.

In order to investigate the isomerization and stability of the various isomers of sulfamide **2.21c** (**Figure 2.7**), each component was isolated and then stirred in water at pH 7; the quantity of each isomer present was then evaluated at different time intervals. The pure α-pyranose anomer **2.21c** gave only a minimal amount of the other isomers after 48 hours (**Figure 2.8**).

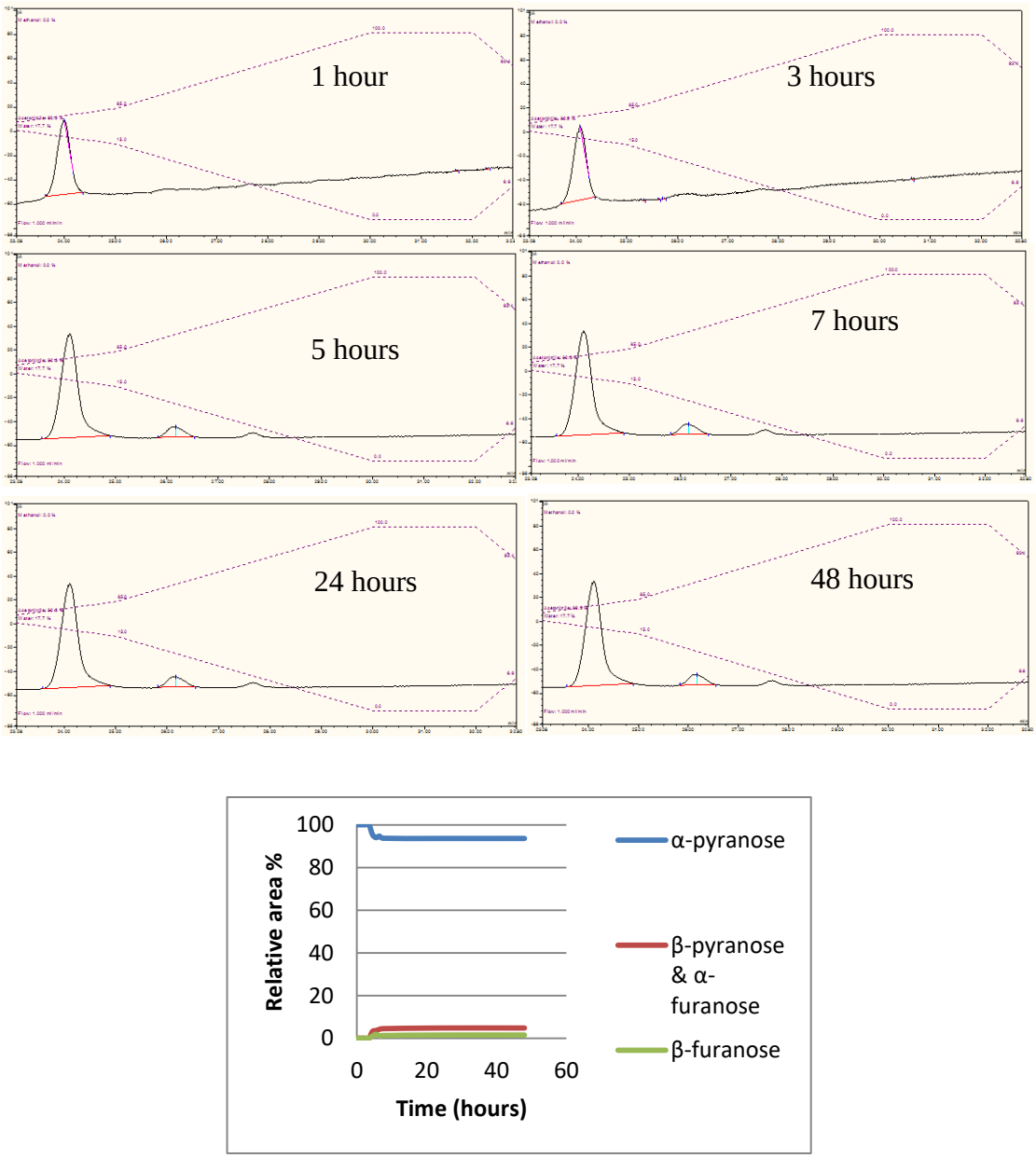


Figure 2.8 RP-HPLC traces and time-dependence of equilibration of *N*-(decyl)-*N'*-(α-D-arabinopyranosyl)sulfamide **2.21c** in water.

However, the aqueous solution of other isomers, the α-furanose/β-pyranose mixture (**Figure 2.9**) and the pure β-furanose form (**Figure 2.10**) all underwent isomerization and produced mixtures in which 70 % of the α-pyranose isomer **2.21c** was present as the major product after 48 hours at rt. The isomerization studies revealed that mutarotation and interconversion of the deprotected α-, β-furanose and β-pyranose sulfamides were rapid (less than one hour) in neutral aqueous solution.

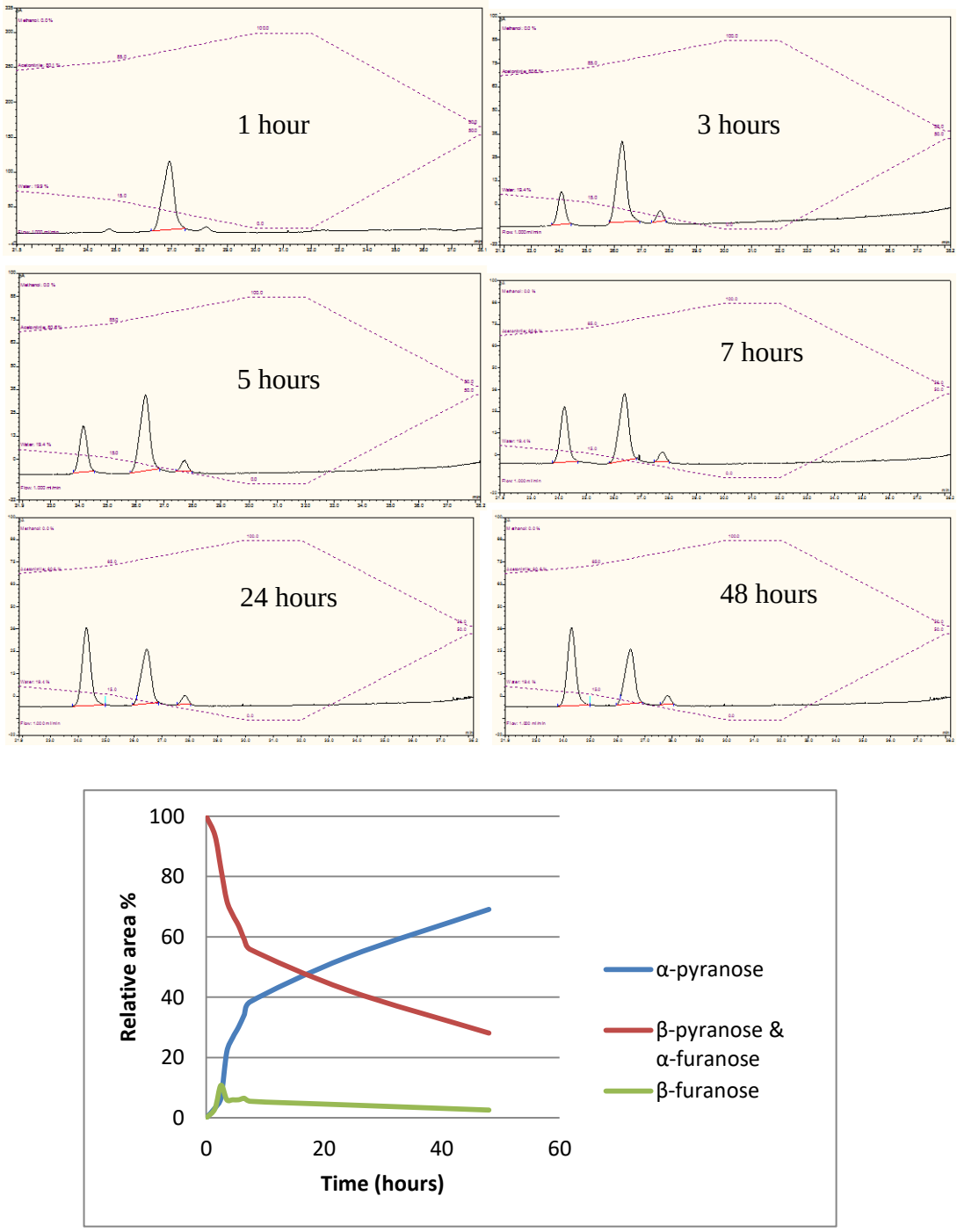
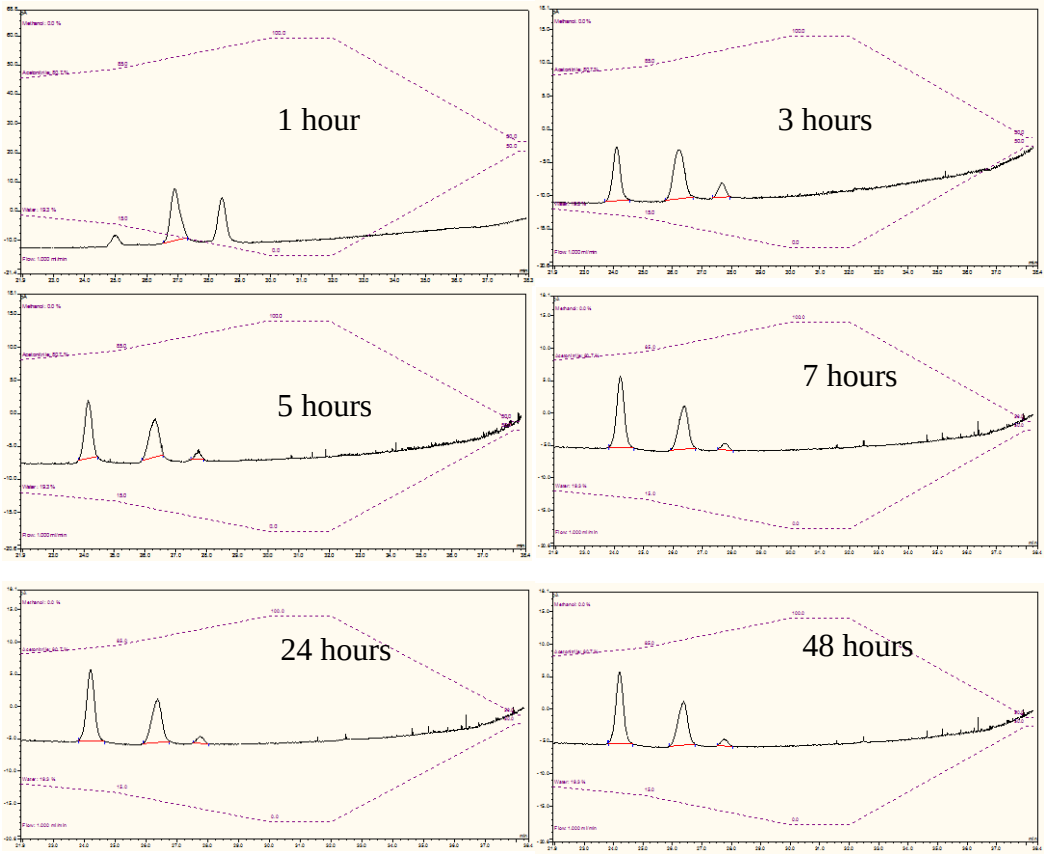


Figure 2.9 RP-HPLC traces and time-dependence of equilibration of *N-(*decyl)-*N'*-(β-D-arabinopyranosyl)sulfamide **2.22a** and *N-(*decyl)-*N'*-(α-D-arabinofuranosyl)sulfamide **2.22b** in water.



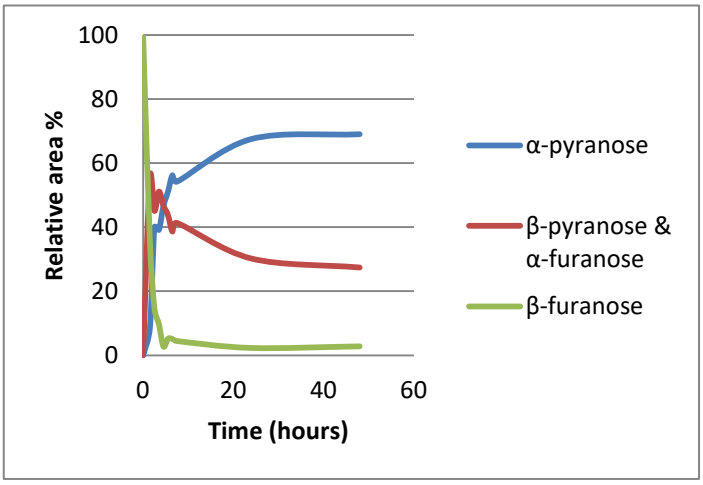


Figure 2.10 RP-HPLC traces and time-dependence of equilibration of *N*-(decyl)-N'-(β-D-arabinofuranosyl)sulfamide **2.22c** in water.

X-ray crystallographic studies revealed that sulfamide **2.21c** adopted $^{1}C_{4}$ conformation with the anomeric nitrogen in an equatorial position; which should be favoured by an $n_{N10} \rightarrow \sigma^{*}_{C2\text{-}O1}$ (**Figure 2.6**) orbital interaction (an exo-anomeric effect). Furanose/pyranose equilibration involves the ring opening of the furanose form to give acyclic *N*-sulfonyl imine/iminium ion intermediates (**Figure 2.11**). Kiessling et al.[94] provided evidence for this type of iminium ion intermediate in the isomerization of UDP-galactopyranose and UDP-galactofuranose catalyzed by the UDP-galactopyranose mutase (UGM) enzymes that are essential for many pathogenic species of bacteria.

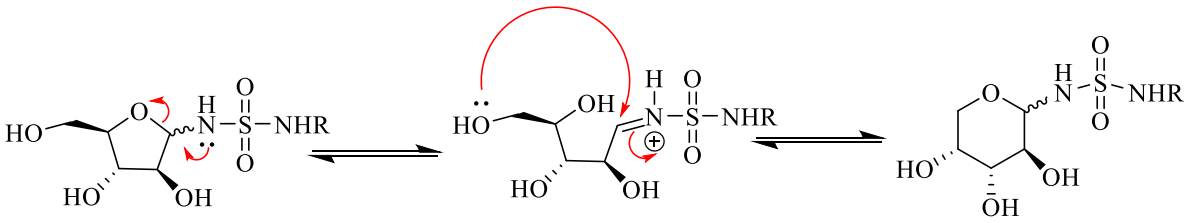
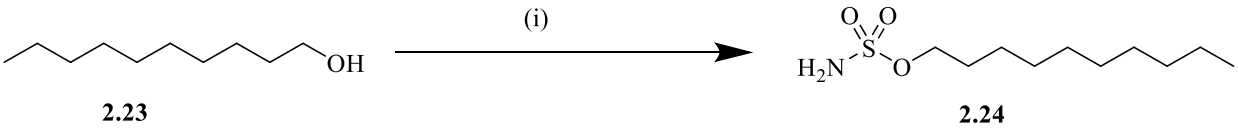


Figure 2.11 Putative mechanisms for pyranose-furanose isomerization of methyl sulfonamide.

The above mutarotation/isomerisation studies demonstrated that α-pyranose *N*-glycosyl sulfamides are thermodynamically the more stable isomers in aqueous solution. A similar result was observed upon de-protection of all compounds **2.20a-m**; in each case a mixture of anomers was produced, and the α-pyranose isomer **2.21a-m** was isolated by RP-HPLC as the major product.

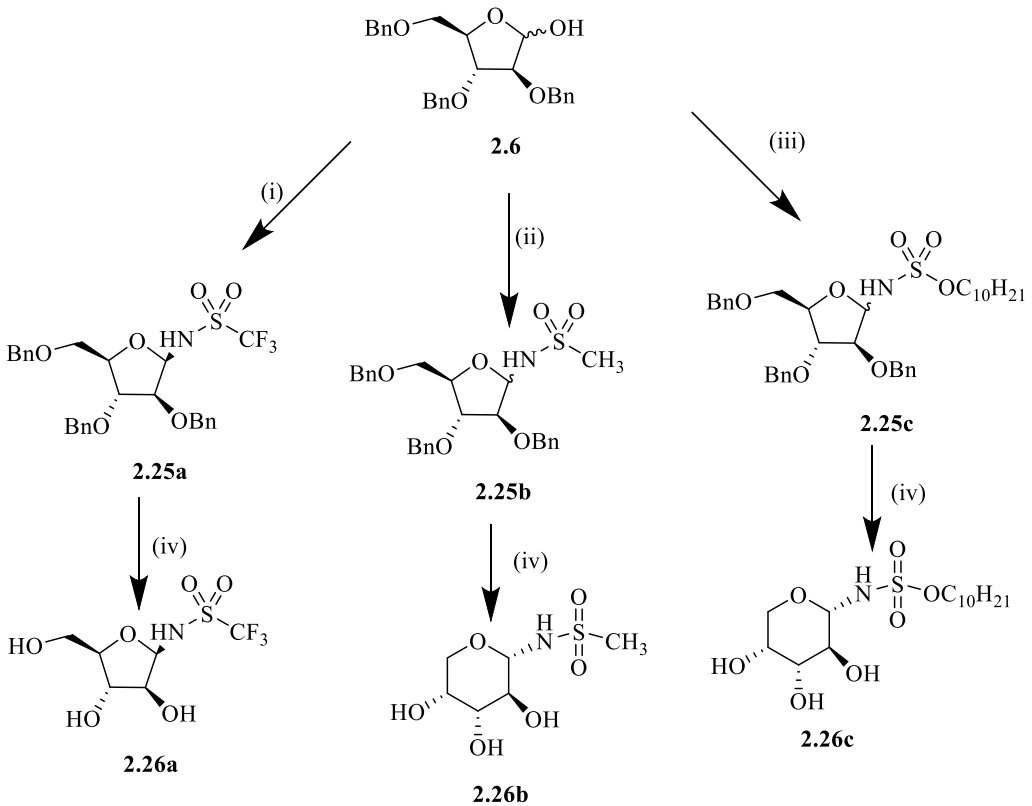
2.3 Synthesis of arabinose *N*-glycosyl sulfonamides and sulfamates

In order to synthesize and also investigate the potential isomerization of *N*-glycosyl sulfonamides and sulfamates, TMS triflate-mediated glycosylations were performed with furanose hemiacetal **2.6** and trifluoromethane sulfonamide, methane sulfonamide, and n-decylsulfamate **2.24** (**Scheme 2.7**) to afford the furanose glycosyl sulfonamides **2.25a** and **2.25b** and the furanose glycosyl sulfamate **2.25c** respectively (**Scheme 2.8**).



2.23 **2.24**

Scheme 2.7 (i) NH_2SO_2Cl, DMA, 0 °C to rt, 3 h, 85 %.



2.6 **2.25a** **2.25b** **2.25c** **2.26a** **2.26b** **2.26c**

Scheme 2.8 (i) TMSOTf, $CF_3SO_2NH_2$, DCM, 0 °C to rt, 16 h, **2.25a** – 44 % (ii) TMSOTf, $CH_3SO_2NH_2$, DCM, 0 °C to rt, 16 h, **2.25b** – 53 % (iii) TMSOTf, $C_{10}H_{21}OSO_2NH_2$, DCM, 0 °C to rt, 16 h, **2.25c** – 56 % (iv) Pd/C, H_2, MeOH, rt, 16 h, **2.26a** – 65 %; **2.26b** – 33 %; **2.26c** – 45 %.

Compounds **2.25a-c** were deprotected by catalytic hydrogenation in the presence of 10% Pd on carbon in MeOH under an atmosphere of hydrogen. Once again upon deprotection of both the methyl sulfonamide **2.26b** and the sulfamate **2.26c** a mixture of anomers was produced, with the major product of these reactions being the α-pyranose isomer. The structure of methyl sulfonamide **2.26b** was confirmed by X-ray crystallography (**Figure 2.12**).

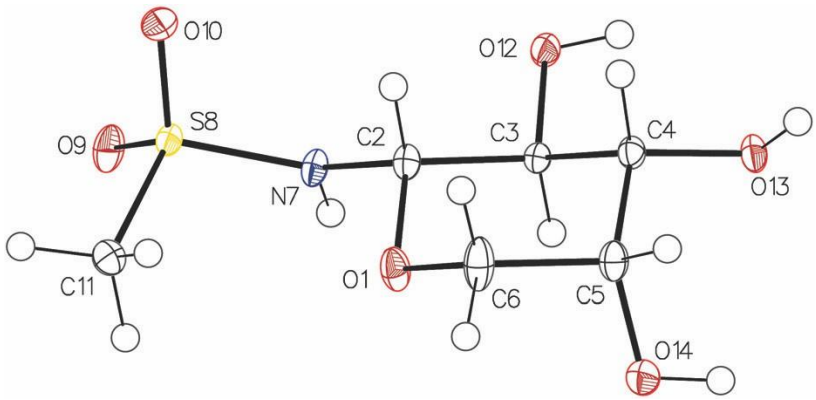


Figure 2.12 X-Ray structure of α-pyranose methyl sulfonamide **2.26b**

As discussed in **Figure 2.11**, the lone pair on the anomeric nitrogen is involved in the facile ring opening of the furanose form. Therefore reasoned that perhaps sulfonamides bearing a strong electron withdrawing group may show a reduced tendency to isomerise. The corresponding *N*-glycosyl trifluoromethanesulfonamide was therefore synthesized by catalytic hydrogenation of **2.25a**, which yielded a single compound, which was identified as the β-furanose isomer **2.26a** and which was found to be configurationally stable in aqueous solution.

2.4 Screening of final compounds as anti-tuberculosis agents

The purified α-pyranose anomers **2.21a-m** were screened as inhibitors of *M. smegmatis* ($mc^2$4517) using the Alamar Blue microplate assay[95,96] to obtain their minimum inhibitory concentration (MIC) values. This assay makes use of Alamar Blue dye, which changes from the oxidized indigo blue non-fluorescent state to the reduced fluorescent pink state in the presence of the growing bacteria (**Figure 2.13**). Compounds that inhibit the growth of the bacteria thus result in a decrease in fluorescence.

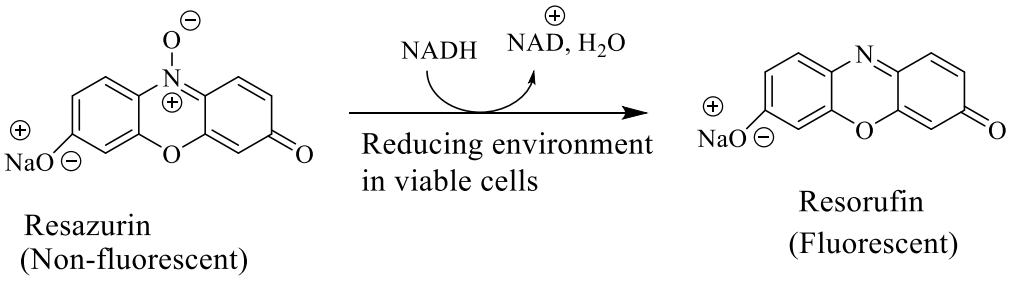
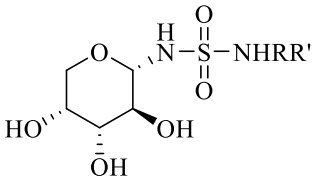


Figure 2.13 Resazurin reduction to resorufin.

The purified test compounds and isoniazid were prepared in DMSO at a concentration of 40 mg/mL, and subsequent 2 fold serial dilutions were performed in 100 µl LB/T media in 96 well microplates, producing compound concentrations of 1000, 500, 250, 125, 62, 31, 15, 7.5, 3.75 µg/mL. Approximately 4.5 x 10^6 CFU/mL of *M. smegmatis* was added to each well to give a total volume of 200 µl. Control wells were also made up that contained only bacteria with 2.5% DMSO in LB/T media. The plates were then incubated at 37 °C for 18 hours. After this time, 10 µl of Alamar Blue dye was added to all wells and the plate was then incubated for another 5 hours. The wells were then observed for a colour change (blue to pink), and the MIC value was determined by visual observation. The results are shown in (**Table 2.1**, **Figure 2.14**).



2.21a-m

Compound	R	MIC (μg/mL)
INH	-	4
2.19c	-	500
2.21a	$-(CH_2)_5CH_3$	> 1000
2.21b	$-(CH_2)_7CH_3$	500
2.21c	$-(CH_2)_9CH_3$	62
2.21d	$-(CH_2)_{11}CH_3$	250
2.21e	$-(CH_2)_{13}CH_3$	> 1000
2.21f	$-[(CH_2)_5CH_3]_2$	125
2.21g	$-[(CH_2)_7CH_3]_2$	500
2.21h	$-[(CH_2)_9CH_3]_2$	> 1000
2.21i	$-[(CH_2)_{11}CH_3]_2$	> 1000
2.21j	$-(CH_2)_2CH(CH_3)(CH_2)_3CH(CH_3)_2$	125
2.21k	$-CH_2CH_2OCH_2CH_2OH$	>1000
2.21l	$-(CH_2CH_2O)_2CH_2CH_2OH$	>1000
2.21m	$-(CH_2CH_2O)_3CH_2CH_2OH$	>1000

Table 2.1 Anti-mycobacterial activity of pyranose glycosyl sulfamides **2.21a-m**.

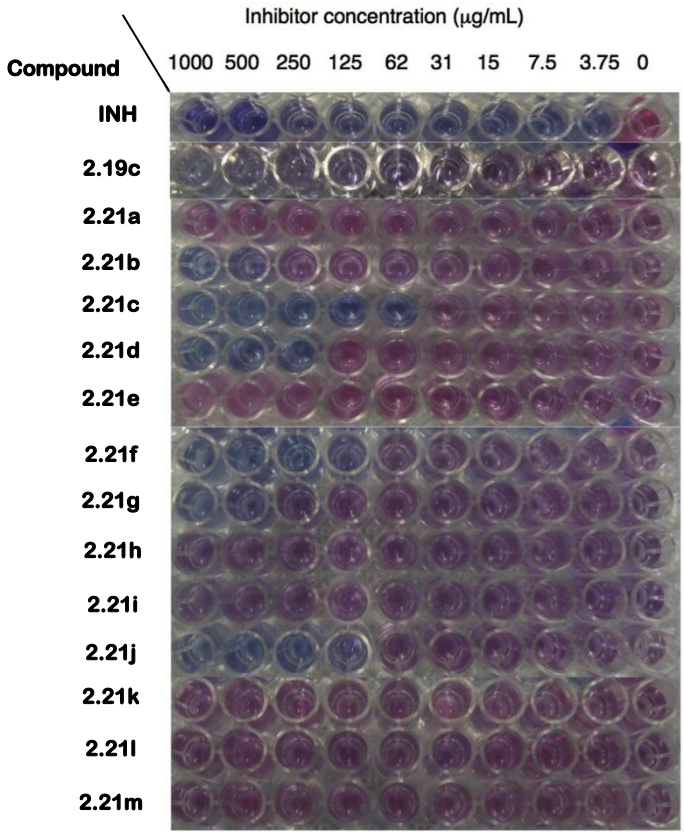
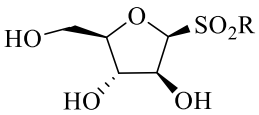


Figure 2.14 Alamar Blue assay of compounds **2.21a-m** plus controls

From the results presented in **Table 2.1**, none of the compounds were very potent inhibitors of mycobacterial growth. Compound **2.21c**, which contains a single alkyl chain of 10 carbon atoms, did show moderate activity (MIC 62 µg/mL). The biological activity increased with the side chain length, and therefore hydrophobicity, was increased from C_6 to C_{10}. Activity then decreased as the number of carbons was further increased from 12 to 14. The results reveal that a correlation exists between the activity of a series of glycosyl sulfones (**Figure 2.15**), previously reported by the Fairbanks group,[64] and these glycosyl sulfamides. The n-butyl sulfone showed only very low activity (MIC 2 mg/mL), but the potency increased with alkyl chain length and reached a maximum for the n-dodecyl sulfone (MIC 62 µg/mL). This sulfone has a total chain length of 13 atoms from the anomeric centre, as is the case for **2.21c**. Subsequently, the activity decreased for sulfones which possessed more extended alkyl chains (**Figure 2.15**). The results demonstrate that a clear correlation exists between structure and biological activity.



R	MIC (µg/mL)
$-(CH_2)_3CH_3$	2000
$-(CH_2)_5CH_3$	500
$-(CH_2)_7CH_3$	250
$-(CH_2)_9CH_3$	125 > X > 62
$-(CH_2)_{11}CH_3$	62
$-(CH_2)_{13}CH_3$	250 > X > 125
$-(CH_2)_{15}CH_3$	125

Figure 2.15 Inhibitory effects of glycosyl sulfones against *M. bovis.*[64]

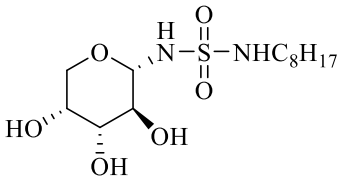
The *N*-Glycosyl sulfamide possessing dialkylated side chains with 6 carbon atoms (**2.21f**) gave an MIC of 125 μg/mL. However, for the dialkyl chain containing sulfamides the activity decreased with increasing chain length from 8 carbon atoms (MIC 500 μg/mL for **2.21g**), to 10 and 12 carbon atoms (MIC > 1000 μg/mL for **2.21h** and **2.21i**). However, in related studies, Von Itzstein had previously reported[65] that *N*,*N*-dihexyl galactofuranosyl sulfonamides, and sulfenamides had lower potency than the *N*,*N*-dioctyl galactofuranosyl sulfonamides, and in the sulfenamides series the *N*,*N*-didecyl derivatives; the reverse of the situation observed here. In that work the *N*,*N*-dioctyl, *N*,*N*-didecyl galactofuranosyl sulfenamides and *N*,*N*-dioctyl galactofuranosyl sulfonamides displayed strong inhibition of mycobacterial growth, with MIC values below 5 μg/mL.

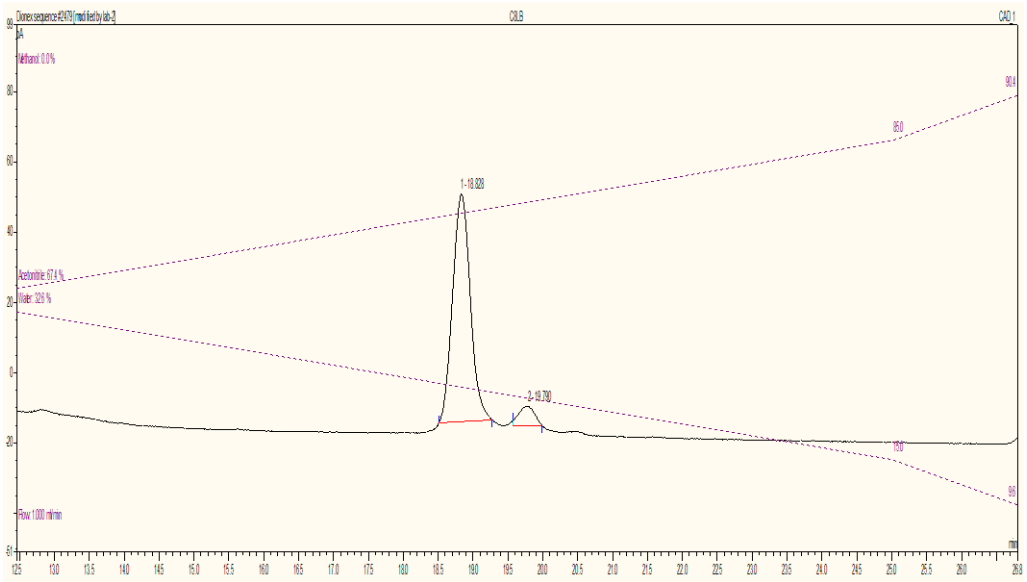
With respect to the other compounds tested, the branched side chain 3,7-dimethyloctyl sulfamide **2.21j** (125 μg/mL) was more active than the straight chain n-octyl sulfamide **2.21b** (500 μg/mL). None of the compounds bearing polyethylene glycol side chains displayed any biological activity at the levels tested (MIC > 1000 μg/mL), possibly due to the increased hydrophilic nature of the side chains. In order to investigate the importance of the carbohydrate moiety, n-decyl sulfamide **2.21c** was also tested against *M. smegmatis*. The activity of the alkyl sulfamide (500 μg/mL) was approximately 8-fold lower than the corresponding glycosyl sulfamide **2.21c** (62 μg/mL) showing that the sugar was important.

As described above, the *N*-glycosyl sulfamides, sulfamates and sulfonamides all undergo mutarotation and furanose/pyranose equilibration in aqueous solution. These AB assays were performed with pure α-pyranose sulfamides. However, other isomers would probably be formed during the assay (> 20 h in duration). HPLC analyses were

performed on compounds **2.21b** and **2.21c** under the AB assay conditions and the amount of isomerisation quantified. The results revealed that only ~ 7% of the α-pyranose sulfamide had converted into a mixture of the β-pyranose and α-furanose forms, and that both isomers are inseparable by HPLC (**Figure 2.16**). Approximately 93% of the material was still in the thermodynamically preferred α-pyranose form. Therefore, it is important to realize that the biological activities reported in (**Table 2.1**) refer to assays of purified α-pyranose compounds, but a minor amount of other isomers was also present at the end of the assay.

Compound **2.21b**

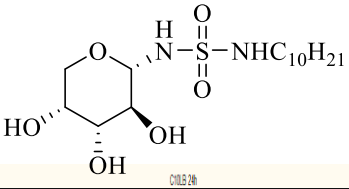


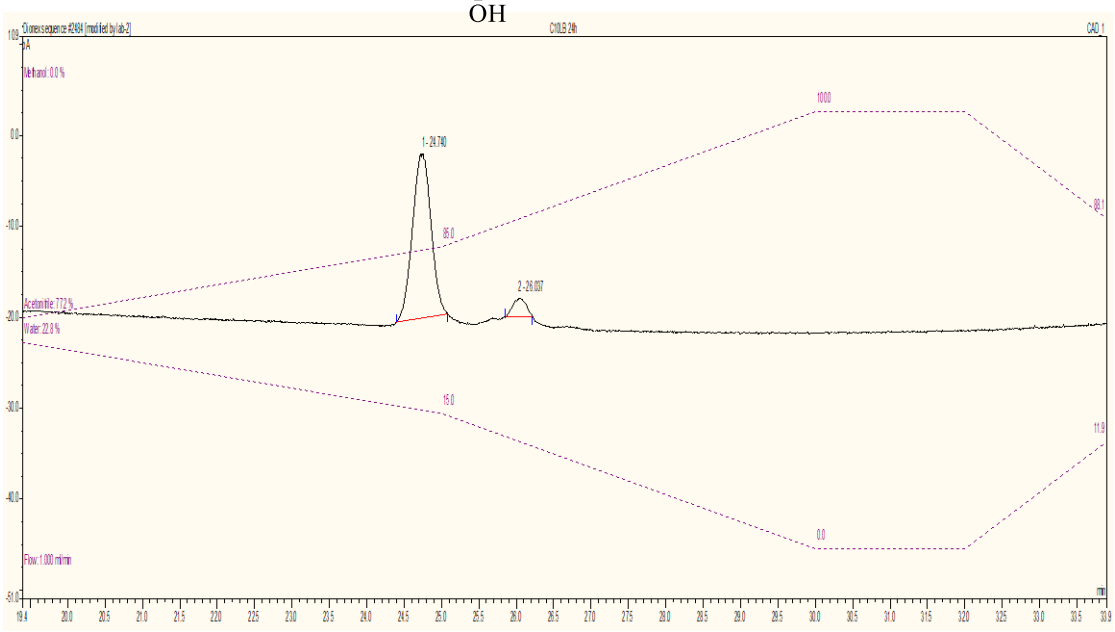


Peak	Ret.Time /min	Height pA	Area pA*min	Rel.Area %	Identity
1	18.83	64.732	19.020	93.00	α-pyranose
2	19.79	5.509	1.432	7.00	β-pyranose and α-furanose
Total:		70.240	20.452	100.00	

Figure 2.16 HPLC trace of compound **2.21b** for the study of isomerization under the AB assay conditions.

Compound **2.21c**





Peak	Ret.Time /min	Height pA	Area pA*min	Rel.Area %	Identity
1	24.74	18.136	5.215	92.75	α-pyranose
2	26.04	2.062	0.408	7.25	β-pyranose and α-furanose
Total:		20.198	5.622	100.00	

Figure 2.17 HPLC trace of compound **2.21c** for the study of isomerization under the AB assay conditions.

The activity of sulfonamides **2.26a-b** and sulfamate **2.26c** were also evaluated as inhibitors of *M. smegmatis* ($mc^2$4517) using an AB assay.

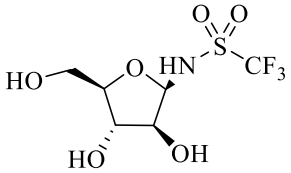
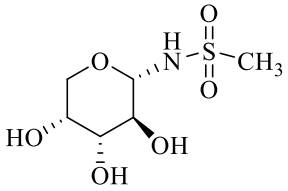
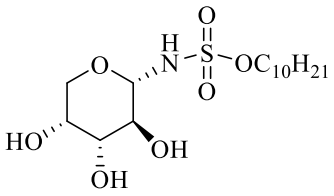
Compound	MIC (µg/mL)
 **2.26a**	>1000
 **2.26b**	>1000
 **2.26c**	125

Table 2.2 Anti-mycobacterial activity of pyranose glycosyl sulfamides **2.26a-c**.

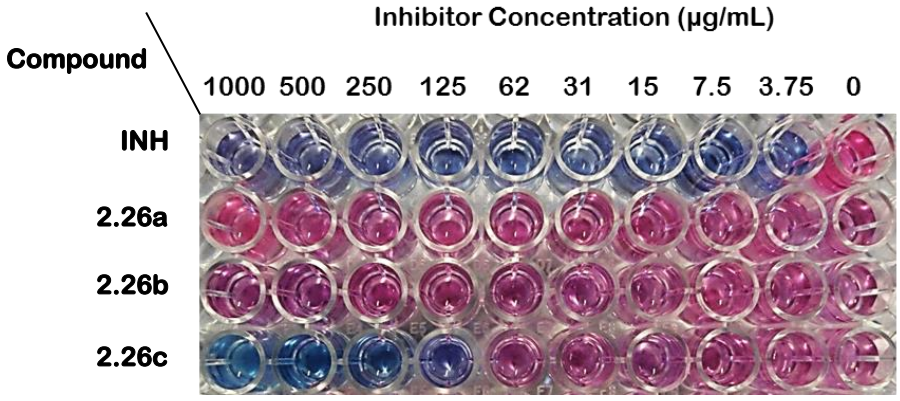


Figure 2.18 Alamar Blue assay of compounds **2.26a-c** plus control

The MIC for the sulfonamides **2.26a** and **2.26b** was greater than 1 mM. The weak activity of the *N*-glycosyl furanose sulfonamide **2.26a** indicates the importance of hydrophobic side chain for anti-mycobacterial activity. The sulfamate **2.26c,** bearing a

C_{10} alkyl chain, showed moderate activity (125 μg/mL) against *M. smegmatis*. The activity of the sulfamate was a factor of 2 lower than the corresponding *N*-glycosylsulfamide bearing a C_{10} alkyl chain **2.21c** (62 μg/mL).

2.5 Synthesis of *N*-glycosyl sulfamides lacking a 5-hydroxyl group

As discussed earlier in this chapter, the attempted synthesis of a variety of glycosyl sulfamides, sulfamates and sulfonamides of arabinofuranose as DPA analogues led to compounds that underwent both mutarotation and furanose to pyranose interconversion. In all cases the major α-pyranose form had shown low to moderate anti-mycobacterial activity. We reason that this may be due to the major component being in the pyranose rather than desired furanose form,.[97]

More positively the crystallographic studies had confirmed that sulfamides had tetrahedral geometry. This interesting motif may therefore be of great value for the design of pharmacological agents using sulfamides as phosphate isosteres of DPA. In order to stop isomerization of the furanose compounds to the thermodynamically more able pyranose form upon de-protection, we undertook the synthesis of a series of *N*-glycosyl sulfamides lacking a hydroxyl group at position-5 of arabinose and evaluated their anti-mycobacterial activity.

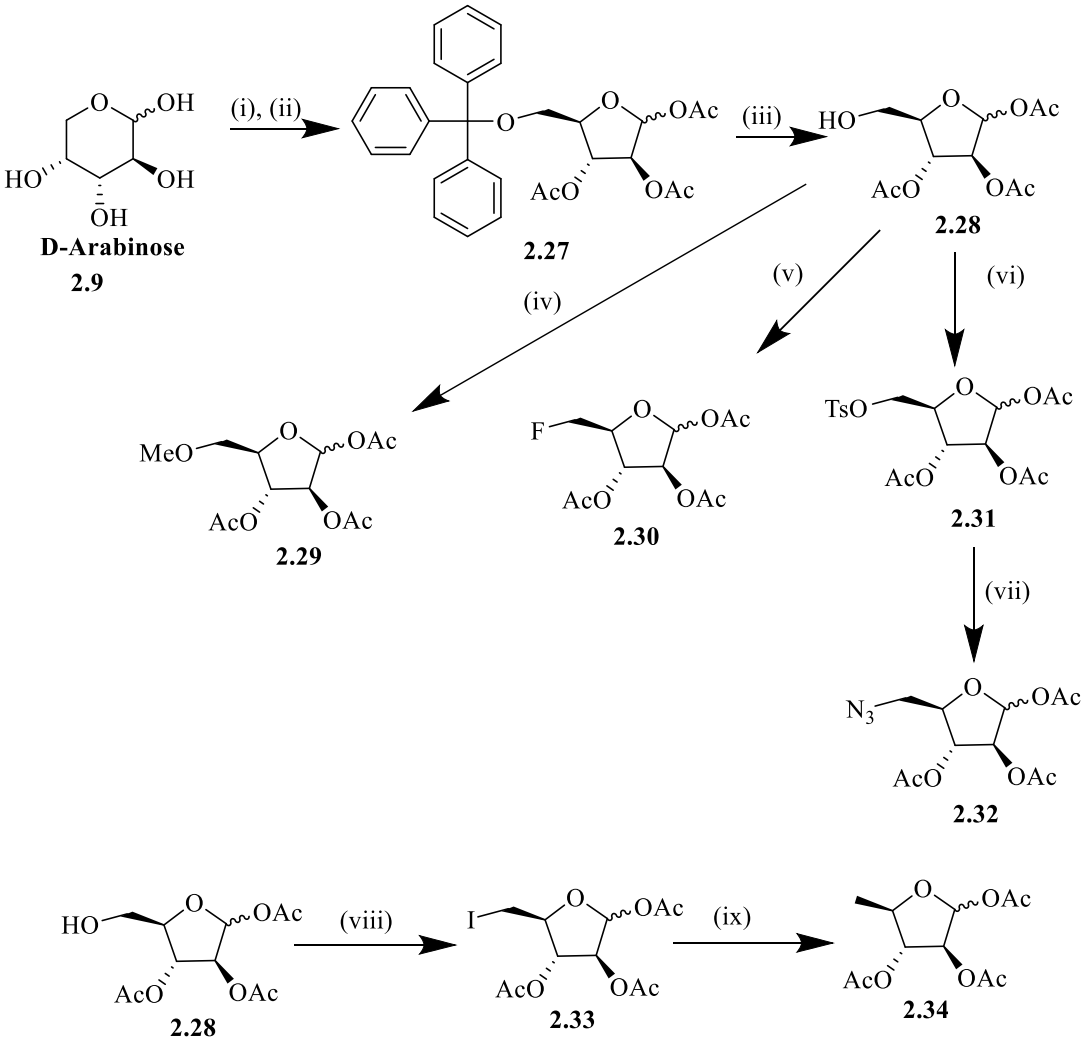
2.5.1 Synthetic strategy

The synthesis of an arabinofuranose donor substrate with modifications at position-5 was to be performed by the same methodology as developed previously by the Fairbanks group.[15] A series of arabinofuranosyl sulfamides were synthesized with a

hydrophobic side chain, wherein the 5-hydroxyl of arabinofuranose was replaced with fluoro, azido, deoxy and methoxy substituents.

Selective modification at position-5 required selective access to position-5. As reported in the literature,[15] commercially available D-arabinose **2.9** was treated with trityl chloride in pyridine at room temperature for 48 h to give the 5-*O*-trityl derivative. The free hydroxyl groups were acetylated using acetic anhydride in pyridine to produce ester **2.27**. Removal of the trityl group was performed without loss of the anomeric acetate by using 80% aqueous acetic acid at 100 °C for 25 minutes, to afford the alcohol **2.28** (**Scheme 2.9**).

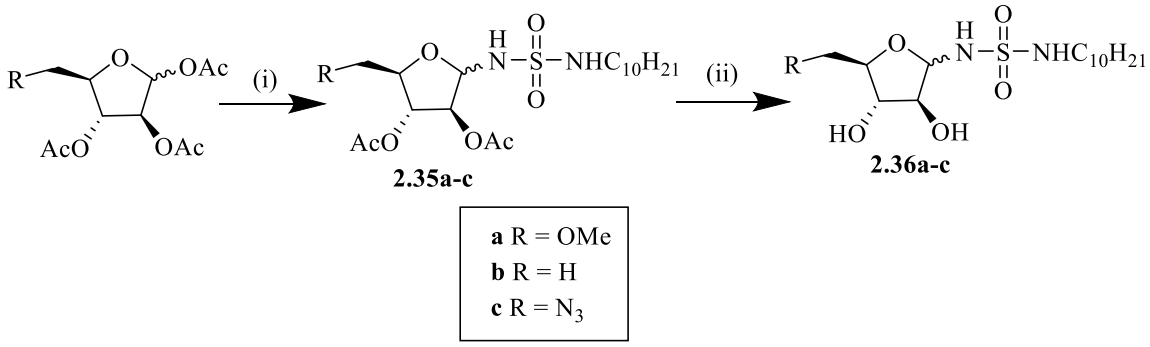
Methylation of free hydroxyl groups at position-5 was achieved by using methyl triflate in the presence of excess di-*tert*-butylmethyl pyridine (DTBMP) and catalytic $Hg(CN)_2$ in dichloromethane to afford the methyl ether **2.29**. Introduction of azide at position-5 was achieved by tosylation of the free hydroxyl group, using tosyl chloride and pyridine at room temperature for 48 hours, to give **2.31** (58 % yield), which was then converted to the azido acetate **2.32** by reaction with sodium azide at 80 °C in DMF. Introduction of fluorine at position-5 was performed by the treatment of alcohol **2.28** with diethylamino sulfur trifluoride (DAST) in diglyme at -40 °C to afford the 5-fluoride **2.30**. 5-Deoxy arabinofuranose was synthesized by de-halogenation. Iodide **2.33** was synthesised by reaction of alcohol **2.28** with triphenylphosphine and iodine in the presence of imidazole using an Appel reaction to give iodide **2.33** which was then reduced by catalytic hydrogenation with Pd/C in the presence of triethylamine to afford the required deoxy arabinofuranose **2.34** (**Scheme 2.9**).



Scheme 2.9 (i) TrCl, pyridine, rt, 48 h, 41 %; (ii) Ac_2O, pyridine, rt, 84 %; (iii) 80% aqueous AcOH, 100 °C, 25 min, 74 %; (iv) MeOTf, DTBMP, $Hg(CN)_2$, DCM, 40 °C, 24 h, 63 %; (v) DAST, diglyme, -40 °C to rt, 16 h, 62 %; (vi) TsCl, pyridine, 48 h, 58 %; (vii) NaN_3, DMSO, 80 °C, 24 h, 56 %; (viii) PPh_3, I_2, imidazole, rt, 2.5 h, 100 °C, 89 %; (ix) 10 % Pd/C, H_2, Et_3N, EtOH, rt, 16 h, 74 %.

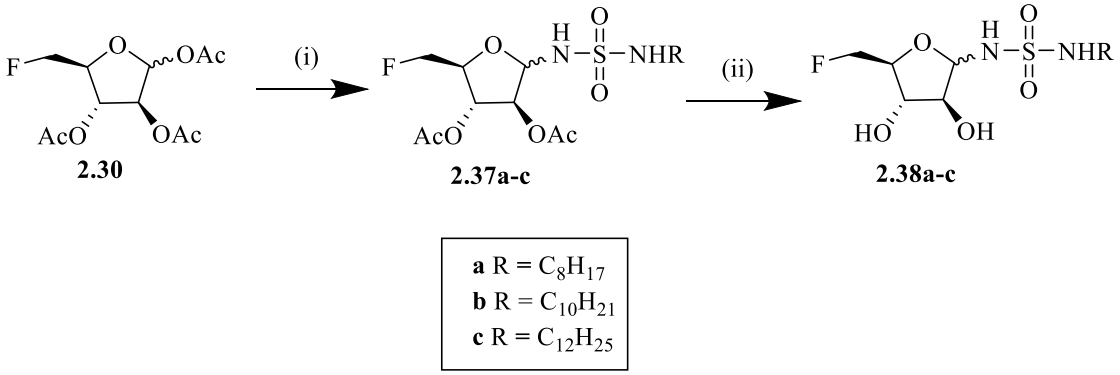
As discussed in the previous section, the C_{10} alkyl chain-bearing pyranose glycosyl sulfamides had revealed optimal anti-mycobacterial activity against *M. smegmatis*.[98] Therefore glycosyl sulfamides bearing a C_{10} chain were synthesized (**Scheme 2.10**) by reaction of glycosyl acetates **2.29**, **2.32** and **2.34** with n-decyl sulfamide in the presence of $BF_3.OEt_2$ at room temperature in DCM, which led to the formation of

corresponding glycosyl sulfamides **2.35a-c**, in each case as an inseparable mixture of anomers (α:β 1:1). Cleavage of the acetates under Zemplen conditions yielded the then corresponding diols **2.36a-c**. The structure of the final compounds was confirmed by coupling constant data of the anomeric position NOE experiment. The α-arabinofuranosides are characterized by $^{3}J_{1,2}$ = 0-3 Hz and an NOE between H-1 and H-3. Whereas β-arabinofuranosides are characterized by $^{3}J_{1,2}$ = 4-5 Hz and NOE was observed between H-1 and H-2, H-4, no NOE was observed between H-1 and H-3.



Scheme 2.10 (i) $BF_3.OEt_2$, $C_{10}H_{21}NHSO_2NH_2$, DCM, rt, 16 h, **2.35a** – 75 %; **2.35b** – 57 %; **2.35c** – 56 %; (ii) Na/MeOH, rt, 16 h, **2.36a** – 82 %; **2.36b** – 81%; **2.36c** – 62 %.

In order to assess any effects of alkyl chain lengths on the biological activity of these compounds three different 5-fluoro glycosyl sulfamides were synthesized (**Scheme 2.11**). Thus, fluoride **2.30** was treated with n-octyl, n-decyl and n-dodecyl sulfamides in the presence of $BF_3.OEt_2$ at room temperature in DCM to give corresponding glycosyl sulfamides **2.37a-c**, again as inseparable mixtures of anomers (α:β 1:1). Cleavage of the acetates under Zemplen conditions yielded the corresponding diols **2.38a-c**.



Scheme 2.11 (i) $BF_3.OEt_2$, $RNHSO_2NH_2$, DCM, rt, 16 h, **2.37a** – 53 %; **2.37b** – 61 %; **2.37c** – 52 % (ii) Na/MeOH, rt, 16 h, **2.38a** – 75 %; **2.38b** – 72 %; **2.38c** – 78 %.

2.5.2 Biological activity

The biological activity of all of the *N*-glycosyl sulfamides with functionalization at position-5 was tested against *M. smegmatis* by using an Alamar Blue assay.[99] Isoniazid (4 μg/mL), ethambutol (0.5 μg/mL) and n-decyl sulfamide **2.19c** were assayed as controls. The n-decyl glycosyl sulfamides **2.36a-c** and **2.38b** with different functional groups at position-5 displayed significant anti-mycobacterial activity, with all four displaying MIC values of 31 μg/mL. The activity did not appear to depend on the modification at position-5. Furthermore, n-decyl sulfamide ($NH_2SO_2NHC_{10}H_{21}$) **2.19c** gave a MIC value of 500 μg/mL. These results demonstrate that the arabinofuranose ring plays a significant role in the biological activity; the activity was enhanced by more than two orders of magnitude as compared to the sulfamide without the sugar. Interestingly, the previously reported pyranose n-decylsulfamidoglycoside **2.21c**, possessing an unmodified hydroxyl group at position-5 (MIC 62 μg/mL) was two times less activity than all of these furanose n-decylsulfamidoglycosides.

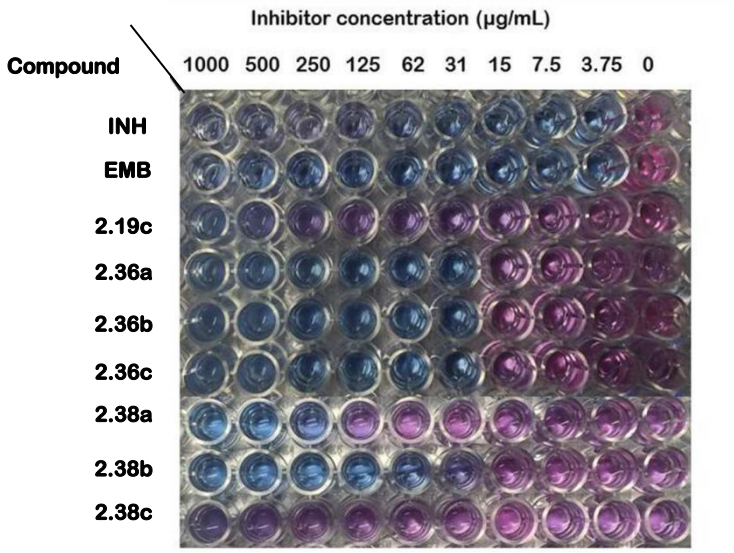


Figure 2.19 Alamar Blue assay of compounds **2.36a-c** and **2.38a-c** plus controls.

Compound	MIC (µg/mL)[a]	MIC (µM)[a]
Isoniazid (**INH**)	4	29
Ethambutol (**EMB**)	0.5	1.8
$NH_2SO_2NHC_{10}H_{21}$ **2.19c**	500	2117
2.36a	31	81
2.36b	31	88
2.36c	31	79
2.38a	250	731
2.38b	31	84
2.38c	1000	2511

[a] MIC = minimum inhibitory concentration; the lowest concentration of the compound which inhibited the growth of *M. smegmatis* >90% in the Alamar Blue assay. Isoniazid (**INH,** MIC 4 µg/mL) and decylsulfamide **2.19c** were used as controls.

Table 2.3 Anti-mycobacterial activity of glycosyl sulfamides.

As reported earlier in this chapter, the alkyl chain lengths influence the anti-mycobacterial activity of these compounds. The activity of the 5-fluoro arabinofuranose glycosyl sulfamides with varying alkyl chain lengths (C_8, C_{10} and C_{12}) was investigated. Sulfamide **2.38a**, with a C_8 alkyl chain, gave a MIC of 250 µg/mL, and was an order of magnitude less active than the C_{10} derivative **2.38b** (MIC

31 μg/mL). Interestingly, these results showed correlation with the previously reported results for the pyranose glycosyl sulfamides and the glycosyl sulfones,[64] in which maximal activity was observed with a total chain length of 13 atoms from the anomeric centre, as is the case for **2.36a-c** and **2.38b**. The activity was significantly reduced by increasing the side chain length to 12 carbon atoms as in compound **2.38c** (1000 μg/mL). Interestingly the pyranose n-dodecylsulfamidoglycoside **2.21d** (250 μg/mL) was 4 times more active than the corresponding 5-fluoro furanose form **2.38c**.

2.6 Conclusions

A wide variety of *N*-glycosyl sulfamides, sulfonamides, and sulfamates of arabinose were synthesized. Unexpectedly, the de-protected materials isomerized from the furanose to the pyranose form in an aqueous solution, to produce mixtures in which α-pyranose form was thermodynamically preferred. In contrast, deprotected *N*-glycosyl trifluoromethane sulfonamide was shown to be configurationally stable in aqueous solution. All compounds were tested for anti-mycobacterial activity using the Alamar Blue microplate assay. Biological testing of the purified α-pyranose sulfamides, methanesulfonamide and sulfamate revealed low to moderate activity against *M. smegmatis.* To remedy the problem of furanose/pyranose equilibration, a series of glycosyl sulfamides which lacked the 5-hydroxyl group were synthesized in order to fix these compounds in the furanose form. These furanose sulfamides were then tested for anti-mycobacterial activity and displayed moderate activity, with a MIC of 31 μg/mL for the C_{10} hydrophobic side chain.

Chapter 3 Synthesis of thymidine monophosphate analogues as potential inhibitors of mycobacterial cell wall biosynthesis

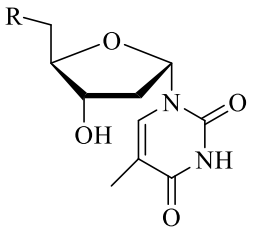
3.1 Introduction

As discussed in previous chapters, the need for long duration treatment and the emergence of multi- (MDR-TB) and extensively drug resistant (XDR-TB) forms of *M. tuberculosis* present significant challenges for the treatment of tuberculosis. [88, 90] The discovery of new mycobacterial targets, and the shortening of current treatment durations are essential for treating MDR-TB and XDR-TB. The recently discovered enzyme *Mycobacterium tuberculosis* thymidine monophosphate kinase (TMPK*mt*) is indispensable for growth and survival of *M. tuberculosis*, as it plays an essential role in DNA synthesis.[75] Therefore, it is an attractive target for the design of novel anti-tuberculosis agents.

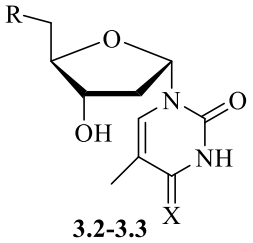
TMPK*mt* catalyses the phosphorylation of thymidine monophosphate (dTMP) to give thymidine diphosphate (dTDP) using ATP as phosphoryl donor, and is essential for maintaining the thymidine triphosphate pool, which is required for DNA synthesis and replication of bacteria. This phosphorylation step is situated at the junction of the *de novo* and salvage pathways for the synthesis of thymidine triphosphate (dTTP).[80,81] TMPK*mt* has low (22%) sequence identity with the human isozyme, and therefore represents a promising target for the development of selective inhibitors.[79]

Inhibitors of TMPK*mt* have previously been reported by Calenbergh *et al*.[79-81, 87, 100] and several others.[101] 5'-Thiourea-substituted α-thymidine derivatives **3.1** were synthesised by Calenbergh *et al.*[102] The analogous 3-trifluoromethyl-4-chlorophenylthiourea **3.2** moiety displayed promising inhibitory activity, with a K_i of

0.6 µM, and an MIC_{99} value of 20 µg/mL against *M. bovis*. In addition, 5'-arylthiourea 4-thio-α-thymidine **3.3** revealed significant inhibition of TMPK*mt* (K_i = 0.17 µM), and was capable of inhibiting *M. bovis* at MIC of 25 µg/mL.[80]



3.1



3.2-3.3

3.2 R = 3-CF_3-4-Cl-Phenylthiourea, X = O
3.3 R = 3-CF_3-4-Cl-Phenylthiourea, X = S

The synthesis and biological activity of sulfonamides and sulfamates has been widely reported, but there are only a few reports on the use of sulfamides as a phosphate isostere. For example Aldrich *et al.*[74,73] reported the use of sulfamide as an isosteric replacement for phosphate in the search for anti-mycobacterial agents as inhibitors of siderophore biosynthesis; salicyl sulfamoyl adenosine and its derivatives displayed promising inhibitory activity, with MICs ranging from 0.19-6.25 µg/mL against *M. tuberculosis*. These adenosine analogues disturb siderophore biosynthesis by inhibition of an adenylate-forming enzyme MbtA, which is involved in biosynthesis of the mycobactins.

As mentioned in the previous chapter, our crystallographic studies confirmed that sulfamides adopt a tetrahedral geometry. This interesting motif could therefore be of great value for the design of pharmacological agents using sulfamides as phosphate isosteres. It was therefore thought worthwhile to investigate the design and synthesis of sulfamides as analogues of thymidine monophosphate. Possible sulfamide structures were screened *in silic*o using induced-fit docking methods.[103] From the docking results, a selection of compounds was synthesized and evaluated for any anti-mycobacterial activity against *M. smegmatis.*

3.2 Molecular docking and structure-based drug design of thymidine monophosphate analogues

Molecular modeling has been of great value in the fields of drug design, computational biology and material science.[104] Molecular docking methods explore ligand conformation and binding affinities, and also estimate the ligand-receptor binding free energy using scoring functions.[103,105] There are two types of docking methods which are widely used in drug design:

a) Lock and key\rigid docking

b) Induced fit\flexible docking

In rigid docking, the conformation of the receptor is fixed, and docking of the molecule of interest is then performed. In contrast, induced-fit docking performs docking calculations with multiple receptor conformations. A small library of sulfamide analogues of TMP was designed and screened with the published three-dimensional structure of TMPK*mt* (PDB accession code: 1N5K)[106], using an induced fit docking method with Schrödinger Suite 2006[107,108] by Dr. Wanting Jiao as detailed below.

3.2.1 Docking preparation and settings

The three-dimensional crystal structure of TMPK*mt* in complex with dTMP substrate was imported from the PDB (accession code: 1N5K).[106] TMPK*mt* is a homodimer and each monomer has 214 amino acids.[109] The receptor structure was prepared in the semi-closed state, which is more representative of the active site conformation when substrate is bound. Protein preparation wizard (most frequently used tools and techniques in structure preparation)[110] was used to add hydrogens, assign bond orders, create zero-order bonds to metals, and fill in missing side chains. Only two water

molecules that coordinate to the metal ion were kept in the structure; all other water molecules were removed. The receptor structure was refined by sampling water orientations and assigning hydrogen bonds. Protonation states were also assigned using PROPKA.[111] Then the structure was minimized with a convergence of heavy atoms set to a root-mean-square deviation (RMSD) of 0.30 angstroms, which is a measure of average atomic distance between the atoms. The receptor grid was generated in glide using co-crystallized ligand (dTMP) to define the centre of the grid box.[110] All other settings were kept as default.

The target compounds were built in Maestro,[112] and prepared using LigPrep.[113] The ligands were then docked into the receptor grid file using glide with the XP (extra precision) mode,[105] The predicted binding poses for each compound were then examined.

The substrate dTMP adopting a C2'-endo confirmation in the active site, which was docked back in the active site to validate the docking procedure and confirmed that the binding mode of the substrate could be successively reproduced by docking calculations.[106]

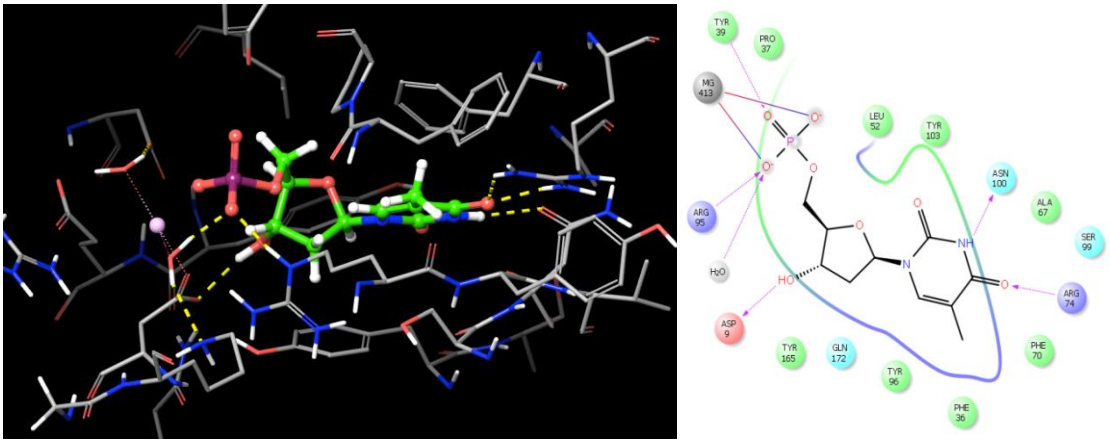
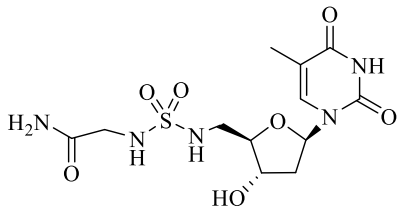


Figure 3.1 Docking of dTMP in the active site of TMPK*mt* (PDB: 1N5K).

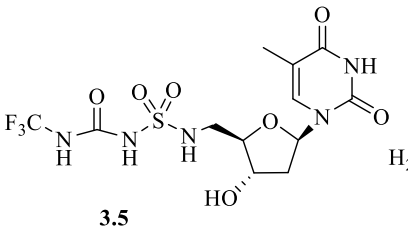
The active site of TMPKmt contains a Mg^{2+}, a water molecule, and residue Arg95, which interact with the non-bridging oxygen of the phosphate moiety of dTMP. Docking studies revealed that the main interactions between dTMP and the enzyme include a stacking interaction between the pyrimidine ring of thymine and Phe70, as well as H-bonds formed between the carbonyl and amino groups of dTMP and the side chains of Arg74 and Asn100 respectively. Another H-bond is formed between the 3'-OH of the 2-deoxyribose and the terminal carboxyl of Asp9 (**Figure 3.1**). These enzyme-substrate interactions therefore suggested that substrate-based competitive inhibitors could be designed by replacement of the 5'-phosphoryl group with a suitable isostere, for example a sulfamide.

3.2.2 Induced fit docking of the target sulfamide derivatives

In order to investigate the binding affinity of the sulfamide derivatives, the following target compounds were docked into the TMPK*mt* active site using the induced fit docking method, and the docking scores (glide score) were listed in **Table 3.1**.



3.4



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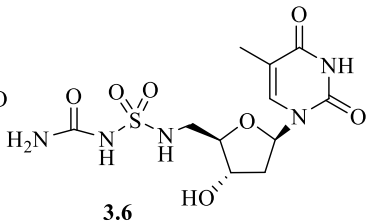

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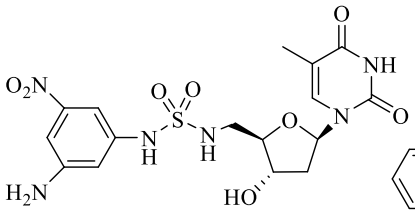

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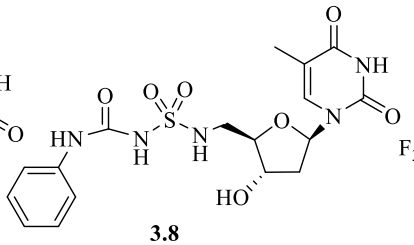

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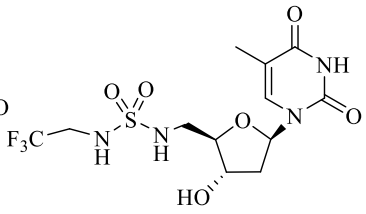

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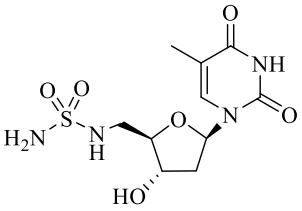
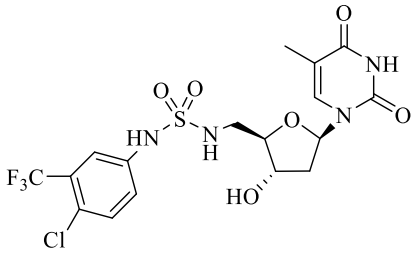


3.10



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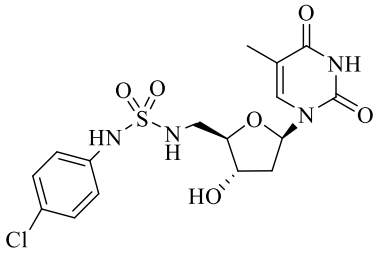

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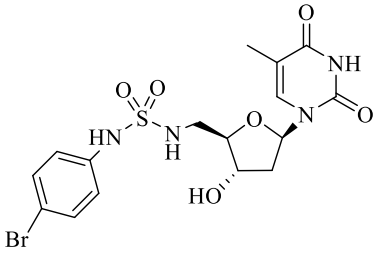

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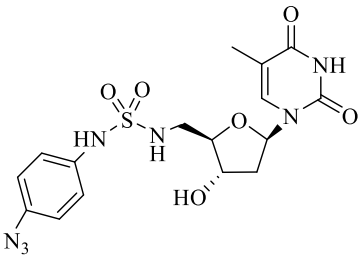
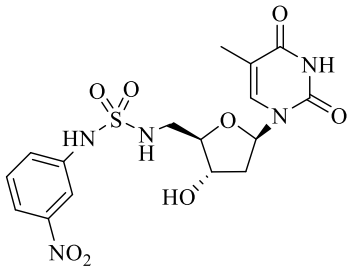


3.14



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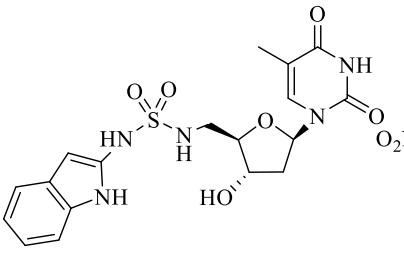

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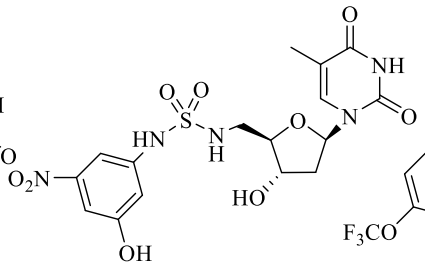

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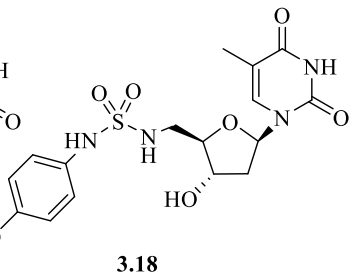

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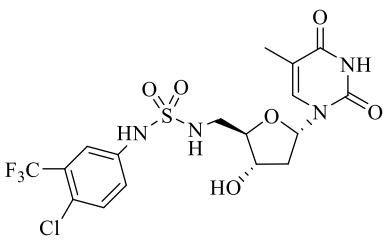

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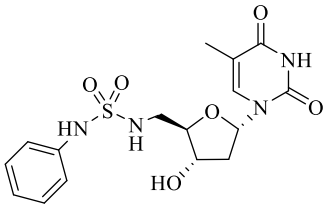
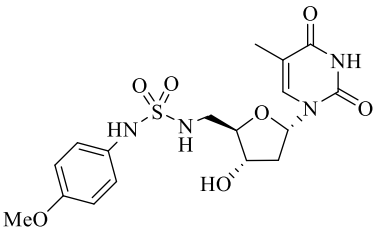


3.20



3.21

Compounds	Glide gscore (kcal/mol)
Substrate dTMP	-14.611
3.4	-11.856
3.5	-12.233
3.6	-12.375
3.7	-11.982
3.8	-11.526
3.9	-10.981
3.10	-12.153
3.11	-11.594
3.12	-12.341
3.13	-12.074
3.14	-11.846
3.15	-11.784
3.16	-11.560
3.17	-11.922
3.18	-11.771
3.19	-11.331
3.20	-12.649
3.21	-11.189

Table 3.1 Docking results of the dTMP analogues on TMPK*mt*.

The empirical scoring function includes a lipophilic-lipophilic term, a hydrogen bond term, a rotatable bond penalty, and a contribution from protein-ligand coulomb-van der Waals energies. The glide scoring function is presented in the following equation:[105]

$$\text{XP GlideScore} = E_{coul} + E_{vdW} + E_{bind} + E_{penalty}$$

The above 18 compounds in which phosphate group was replaced by a sulfamide that was modified with attached groups, were all docked to TMPK*mt*.

The docking scores of the compounds ranged from -10.9 to -12.6 kcal/mol. Compound **3.10** gave a docking score of -12.153 kcal/mol. This result implied that the binding affinity of the compound **3.10** would be less than that of the substrate dTMP (-14.611 kcal/mol). As shown in **Figure 3.2**, the sulfamide group of compound **3.10** was placed in close proximity to the phosphate binding site. However, due to the lack of negative charge the sulfamide group did not form strong interactions with Arg95.

The results suggested that adding extra functional groups to the sulfamide would in fact not improve compound binding. However, a few extra interactions were picked up by the some of the additional functional groups. This is because these additional groups are mostly solvent exposed, as there is not enough space to accommodate the extra groups within the active site.

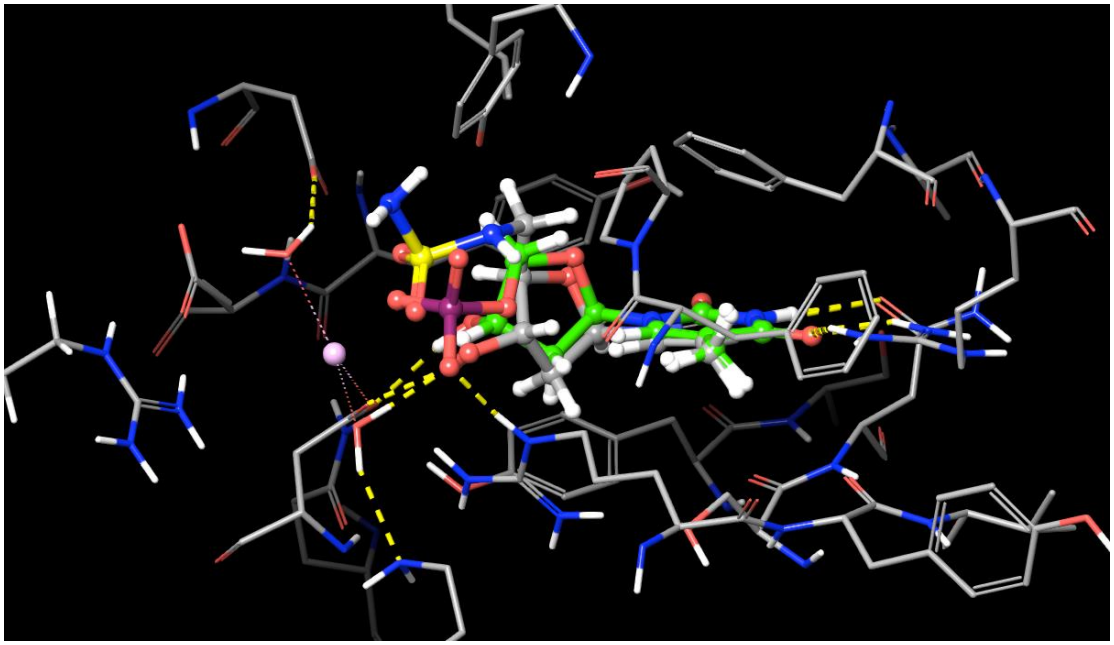


Figure 3.2 Docking of the substrate dTMP (green carbons) and compound **3.10** (grey carbons) in the active site of TMPK*mt*.

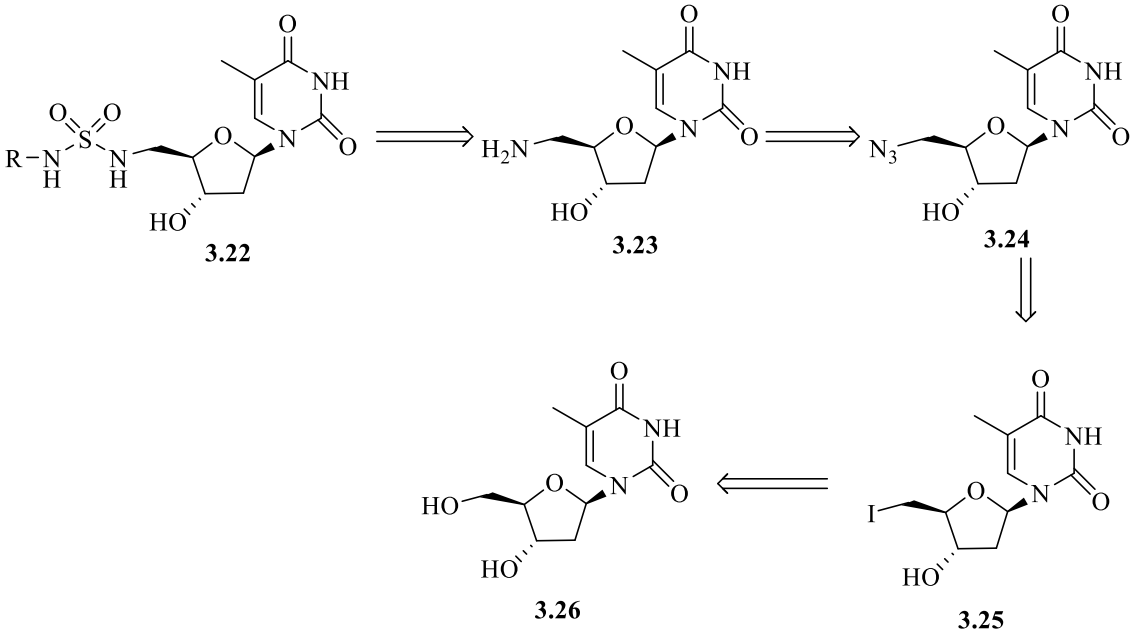
All the compounds, except **3.9**, showed similar binding affinities ranging from -11 to -12 kcal/mol. In order to investigate possible anti-mycobacterial activity of these materials, compounds **3.10**, **3.11**, **3.12**, **3.13** and **3.14** were synthesised and their anti-mycobacterial activity was evaluated against *M. smegmatis*.

3.3 Synthesis of sulfamide derivatives as dTMP analogues

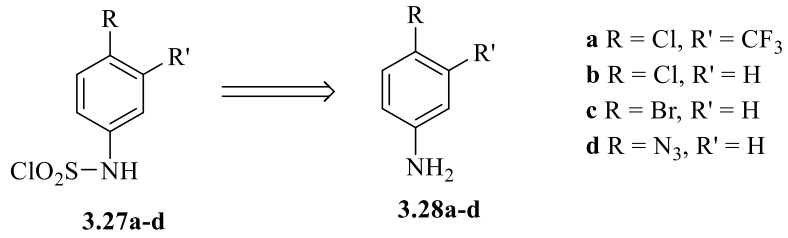
3.3.1 Retrosynthetic analysis

A retrosynthetic analysis of the target compound **3.22** is shown **Scheme 3.1**. Commercially available thymidine **3.26** could be selectively iodinated at position-5, to give an iodide which could then be converted to azide **3.24**. 5-Amino thymidine **3.23** could be synthesised by reduction of azide **3.24**. A selection of target compounds **3.22** could be obtained by the reaction of primary amine **3.23** with the commercially available sulfamoyl chloride and the corresponding aryl sulfamoyl chlorides **3.27a-**

3.27d. The aryl sulfamoyl chlorides **3.27a-3.27d** could be synthesized from the corresponding amines **3.28a-3.28d** (**Scheme 3.2**).

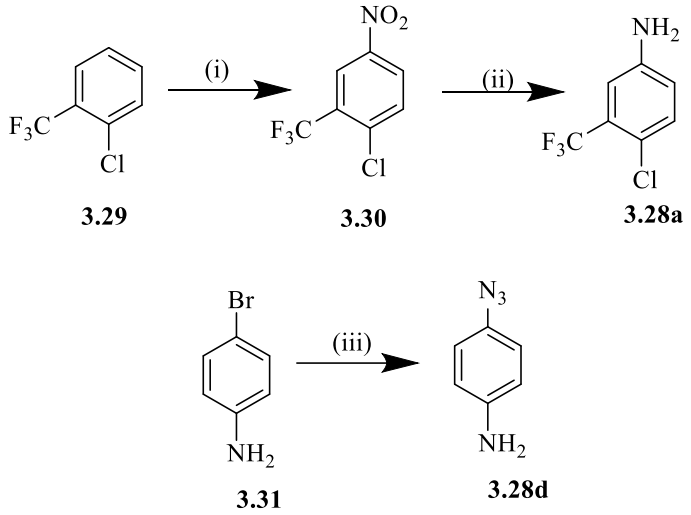


Scheme 3.1 Retrosynthetic pathway for the synthesis of sulfamide derivatives.



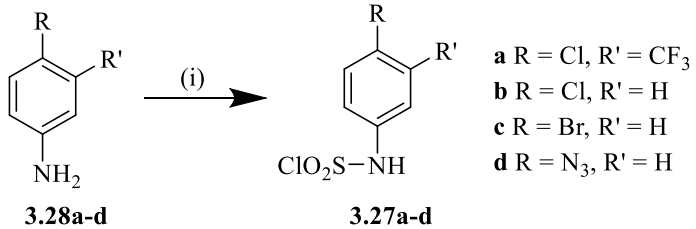
Scheme 3.2 Retrosynthetic pathway for the synthesis of sulfamoyl chlorides.

3.3.2 The synthesis of sulfamoyl chlorides



Scheme 3.3 (i) HNO_3, H_2SO_4, 50-60 °C, 1h, 72 %; (ii) Pd/C, H_2, MeOH, rt, 2 h, 69 %; (iii) NaN_3, CuI, proline, NaOH, EtOH, H_2O, 75 °C, 3h, 48 %.

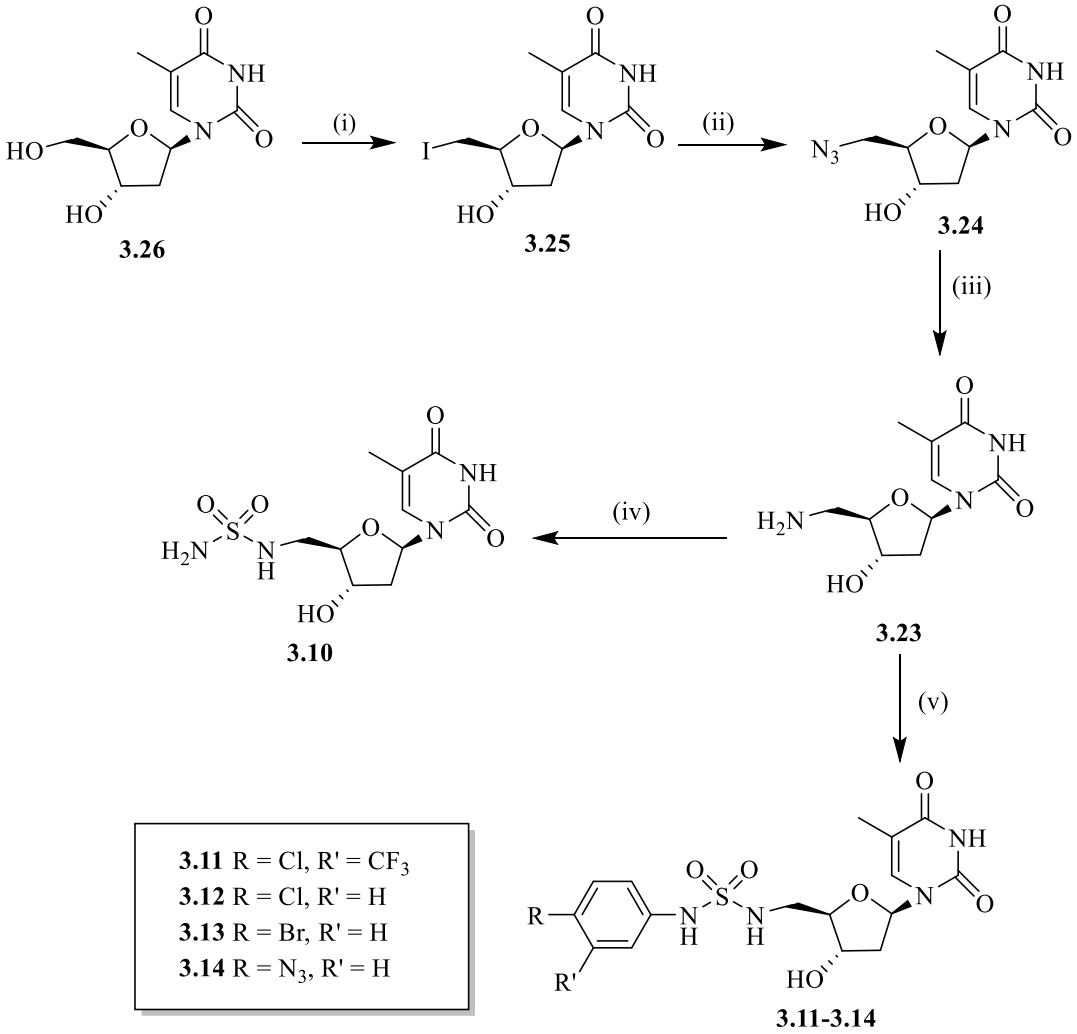
In order to obtain the required sulfamoyl chlorides, the corresponding aniline derivatives were synthesized (**Scheme 3.3**). Nitration of commercially available 4-chlorobenzotrifluoride **3.29** was carried out using a 1:1 mixture of conc. HNO_3 and H_2SO_4 to afford the nitrobenzene **3.30** by electrophilic aromatic substitution.[114] The nitro compound **3.30** was then reduced by catalytic hydrogenation in the presence of 10% Pd on carbon in MeOH under an atmosphere of hydrogen to yield aniline **3.28a**. Alternatively, the aryl azide **3.28d** was synthesized from commercially available 4-bromoaniline **3.31**, using a proline-promoted CuI-catalysed Ullmann-type coupling.[115]



Scheme 3.4 (i) HSO_3Cl, Et_3N, DCM, -9 °C to rt, 1 h; PCl_5, toluene, 80 °C, 2 h.

Sulfamoyl chlorides **3.27a-d** were synthesized from the commercially available amines **3.28b** and **3.28c**, and other amine derivatives **3.28a-3.28d**, by first convertsion into the *N*-sulfonic acid, and then chlorination using PCl_5 to afford the sulfamoyl chlorides **3.27a-d** (**Scheme 3.4**).

3.3.3 The synthesis of target sulfamide derivatives.



Scheme 3.5 (i) PPh_3, I_2, imidazole, THF, 60 °C, 41 % ; (ii) NaN_3, DMF, 50 °C, 70 %; (iii) PPh_3, H_2O, rt, 16 h, 60 %; (iv) NH_2SO_2Cl, Et_3N, DMA, 0 °C to rt, 2 h, 74 %; (v) Et_3N, **3.27a-d**, CH_3CN, 0 °C to rt, 2 h, **3.11** – 65 %; **3.12** – 49 %; **3.13** – 41 %; **3.14** – 34 %.

As shown in **Scheme 3.5**, thymidine **3.26** was used as a starting material. The iodide **3.25** was synthesized *via* selective iodination of the primary alcohol with PPh_3, I_2, and imidazole using an Appel reaction[116]. Azide **3.24** was then made by nucleophilic substitution of **3.25** using NaN_3. This was followed by catalytic hydrogenation in the presence of 10% Pd on carbon in MeOH under an atmosphere of hydrogen to yield amine **3.23**. Amine **3.23** was then sulfamoylated using sulfamoyl chloride and Et_3N to provide sulfamide **3.10**.

Additionally, analogues **3.11-3.14** were synthesized by reaction of amine **3.23** with sulfamoyl chlorides **3.27a-3.27d** and purified by RP-HPLC.

3.4 Biological activity of the sulfamide analogues of dTMP

The biological activity of sulfamide analogues **3.10-3.14** were tested against *M. smegmatis* by using an Alamar Blue assay, using techniques described previously. [99] Ethambutol (MIC 0.5 µg/mL) was also assayed as a control. The visual observation of the AB assay and the MIC values for the inhibitors are shown in **Figure 3.3** and **Table 3.2** respectively.

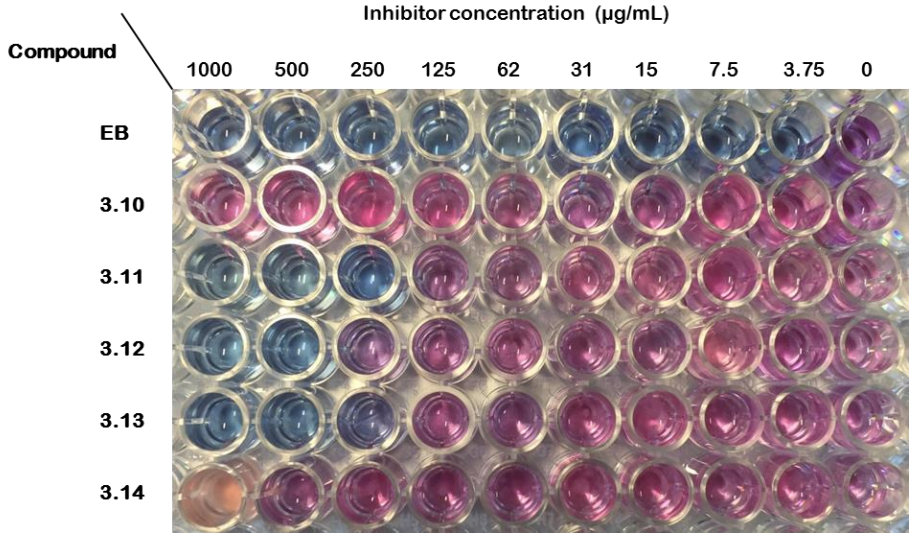


Figure 3.3 Alamar Blue assay of compounds **3.10-3.14** plus control.

Compound	MIC (µg/mL)[a]
Ethambutol (**EB**)	0.5
3.10	>1000
3.11	250
3.12	250
3.13	250
3.14	>1000

[a] MIC = minimum inhibitory concentration; the lowest concentration of the compound which inhibited the growth of *M. smegmatis* >90% in the Alamar Blue assay. Ethambutol (**EB,** MIC 0.5 µg/mL) was used as a control.

Table 3.2 Anti-mycobacterial activity of sulfamide analogues.

From the results presented in **Table 3.2**, none of the compounds displayed potent inhibitory activity against *M. smegmatis*. The sulfamide analogue **3.10** displayed no growth inhibition at concentrations up to 1000 µg/mL, possibly due to the hydrophilic nature of the sulfamide moiety, which may limit membrane permeability. Analogues **3.11-3.13**, which contain a halogenated phenyl ring sulfamide substituent, displayed low activity, with MICs of 250 µg/mL. The activity did not appear to depend on the identity of the halogen substituents on the phenyl ring; namely *p*-chloro, *p*-bromo, or

3-CF_3-4-Cl-phenyl sulfamide. However, the presence of azide functionality on the ring (**3.14**) led to a greater than 4-fold loss in activity against *M. smegmatis* (MIC > 1000 μg/mL). The halogenated phenyl analogues **3.11-3.13** were more than 4 times more active than sulfamide **3.10**. In this series of sulfamide analogues of dTMP, anti-mycobacterial activity was clearly influenced by the nature of the substituent attached to the sulfamide.

As discussed in this chapter, the 5 compounds **3.10-3.14** were docked into the substrate binding site of the TMPK*mt* enzyme. However, the *in vitro* assays demonstrate that no clear correlation exists between anti-mycobacterial activity and *in silico* docking studies.

3.5 Conclusions

A wide variety of sulfamide analogues were designed and docked into the active site of the enzyme TMPK*mt*. All the compounds, except **3.9**, gave similar docking scores, ranging from -11 to -12 kcal/mol. In order to investigate the anti-mycobacterial activity of these compounds, five compounds, **3.10**, **3.11**, **3.12**, **3.13**, and **3.14,** were then synthesised and their anti-mycobacterial activity evaluated against *M. smegmatis*. Aryl sulfamides with halogen substituents at position 5' gave MICs of 250 μg/mL. However, none of the compounds showed inhibitory activity against *M. smegmatis* that was promising enough to merit further investigation.

3.6 Future work

In order to investigate the effects of other functionalities attached to the sulfamide, analogues **3.20** and **3.4-3.6** should be synthesised, and their inhibitory activity evaluated for. Additionally, as Calenberg *et al*.[80] has previously shown that the α-

anomers displayed more promising activity than the β-anomers against TMPK*mt*, the α-thymidine analogues could also be synthesised and evaluated for their anti-mycobacterial activity. Finally a TMPK*mt* inhibitory assay could be developed to determine the binding affinities of these sulfamides to the active site, and in particular to investigate if there is any correlation between binding affinity and the results of the docking studies.

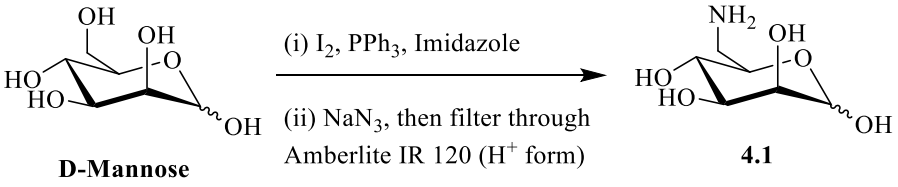
Chapter 4 Efficient reduction of organic azides by sodium iodide in the presence of acidic ion exchange resin

4.1 Introduction

Amines play an important role in the organic synthesis and find wide-reaching applications in many fields. They are widely used in the treatment of diseases, the development of crop protection chemicals, and the production of care products.[117] Furthermore, amines are used in the synthesis of nitrogen containing heterocycles[118] and carbohydrates[119] and in nucleoside chemistry. Among amines, primary amines are central in organic synthesis. One of the existing methods for the preparation of primary amine starts from the corresponding alcohol, which is then transformed into a good leaving group, followed by nucleophilic substitution with azide. The azide is then reduced and to obtain a primary amine. Thus, the azide moiety plays a vital role as a primary amine precursor in organic synthesis.

A wide variety of reduction methods of azides to primary amines have previously been reported.[120] The most prominent method of reduction is the catalytic hydrogenation. However, the reduction method has drawbacks related to its lack of selectivity. The Staudinger reaction using PPh_3[121,122,123] and H_2O also widely used for the azide reduction, however, the drawback of this reaction is the removal of the byproduct $O{=}PPh_3$. In addition, $LiAlH_4$, borohydrides,[124,125,126] metal catalysed hydrogenations,[127] H_2S[128] and radical initiators[120f] have all been widely used for this transformation. The majority of these reductions have some drawbacks related to their functional group tolerance and selectivity, long reaction times and sometimes harsh reaction conditions.

This chapter details the discovery of a new reduction method which was accidentally discovered during the synthesis of 6-amino-D-mannose pyranose, using iodide and Amberlite IR 120 ion exchange resin (H^+ form) (**Scheme 4.1**). During this process, D-mannose was first selectively iodinated at position-6 with I_2, PPh_3 and imidazole using an Appel reaction. The reaction mixture was concentrated *in vacuo*, and then re-dissolved in water. The aqueous layer was then washed with DCM to remove excess PPh_3 and triphenylphosphine oxide (which is a byproduct of the Appel reaction). Then without further purification, the crude 6-iodo-D-mannose pyranoside from the aqueous layer was then reacted with NaN_3. Following that reaction, in order to remove the imidazole, the reaction mixture was filtered through Amberlite IR 120 ion exchange resin (H^+ form), and then concentrated *in vacuo*. Interestingly, the final product was identified as the amine **4.1**, and was purified by RP-HPLC. It was thought that the reduction of azide at position-6 must have occurred in the presence of both the acid and iodide; the latter was formed either during the Appel reaction or by the nucleophilic substitution reaction.



Scheme 4.1 One-step synthesis of 6-amino-D-mannose pyranoside **4.1**.

From a search of the literature, a few reports were found on the use of Lewis Acids in combination with NaI, such as $FeCl_3$/NaI[129], $CeCl_3$/NaI[130], and $BF_3.OEt_2$/NaI,[131] for the transformation of azides to amines. Furthermore, Kamal et al. have reported the chemoselective reduction of aromatic azides catalysed by Al/Gd triflates/NaI.[132]

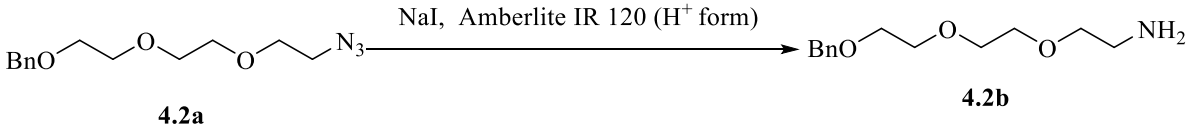
However, this methodology only selectively reduces aryl azides. In addition, NaI/NH_2SO_3H,[133,134] SmI_2[135] and HI[136] have also been reported as reducing agents for azides.

The major disadvantage associated with the use of Lewis Acids is the difficulty in removing the Lewis Acid from the reaction mixture and low functional group tolerance. As a result, there is always considerable interest in the development of a simple and efficient protocol for this organic transformation.

In order to investigate the reduction reaction that had occurred using NaI/Amberlite IR 120 (H^+ form), the reaction conditions were first optimized. The reduction was performed in the presence of different functional groups.

4.2 Optimization of the reduction conditions

As summarized in **Table 4.1**, the reduction was performed at different temperatures and in different solvents. Additionally, the amount of NaI used was systematically increased. Azide **4.2a** was used as a substrate for the optimization of the reduction procedure. Studies commenced with the use of two equivalents of both iodide and acid. Acidic ion exchange resin (Amberlite IR 120, H^+ form) was used as the source of acid. CD_3OD and CD_3CN were used as solvents to enable monitoring of reaction progress by ^1H NMR (**Table 4.1**).



4.2a **4.2b**

Entry	Iodide/ Equiv.	Acid/ Equiv.[a]	Solvent	Time	Temp/ °C	% of 1H-NMR conversion
1	2	2	CD_3OD	1 h	rt	0
2	4	2	CD_3OD	1 h	rt	20
3	4	0	CD_3OD	1 h	rt	0
4	4	2	CD_3OD	1 h	40	45
5	8	2	CD_3OD	1 h	rt	46
6	8	2	CD_3OD	16 h	rt	82
7	8	2	CD_3OD	1 h	40	50
8	10	2	CD_3OD	1 h	rt	65
9	10	2	CD_3OD	16 h	rt	94
10	12	2	CD_3OD	1 h	rt	100
11	12	2	CD_3CN	1 h	rt	90
12[b]	4	2	CD_3OD	0.25 h	40	100

[a] Equivalents were calculated using an exchange capacity for Amberlite IR 120 of 1.8 mequiv./mL wetted bed volume (MeOH). [b] Performed at 200 mbar on a rotary evaporator.

Table 4.1 Conversion of azide **4.2a** into primary amine **4.2b** using NaI and Amberlite IR 120 (H^+ form) under different experimental conditions.

The use of 2 equivalents of NaI and 2 equivalents of acids did not reduce the azide after 1 h at room temperature (**Entry 1**). A two-fold increase in the equivalents of iodide (**Entry 2**) produced amine **4.2b** with 20% conversion. The azide was not reduced at all in the absence of acid (**Entry 3**). When the reaction mixture was stirred at 40 °C for 1 h, product formation was increased by 25% (**Entry 4**) as compared with the reduction at room temperature (**Entry 2**). The efficiency of the reduction was accelerated by increasing the amount of iodide from 8 to 12 equivalents, and also by increasing the reaction time (**Entry 5-9**). Complete conversion to product was observed after 1 h at room temperature by using 12 equivalents of iodide and 2

equivalents of acid (**Entry 10**). In addition, changing the solvent from CD_3OD to CD_3CN reduced the reaction efficiency by only 10% (90% conversion, **Entry 11**).

Nine equivalents of NaI had been used in previously reported reduction methods.[129,130] The use of such a large excess of iodide was undesirable for large scale synthesis. Additionally it is difficult to remove the salts from the highly polar amine products. However, during the accidental discovery of the reduction method (**Scheme 4.1**), complete conversion was observed after the concentration of the crude mixture on a rotary evaporator. In order to investigate the reaction under reduced pressure, the reaction was then performed on a rotary evaporator with 4 equivalents of iodide, 2 equivalents of acid and at a pressure of 200 mbar at 40 °C. This resulted in complete conversion to amine **4.3** after approximately only 15 minutes (i.e. after the solvent had been evaporated to dryness, **Entry 12**).

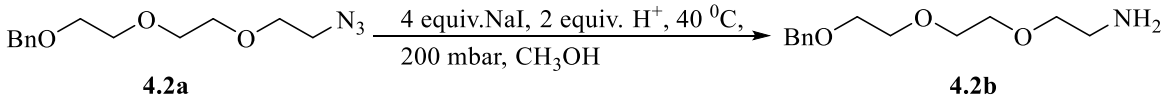
In order to explore the reason for the increase in reduction efficiency on the rotary evaporator, the reaction was performed with varying iodide concentrations at atmospheric pressure. As shown in **Table 4.2**, the reaction was accelerated by increasing the concentration of iodide from 1 M to 4 M. The use of 4 M iodide and 2 equivalents of acid resulted in the complete conversion of azide to amine in 15 minutes at atmospheric pressure.

Entry	Iodide concentration	NaI/ equiv.	Acid/ equiv.	Solvent	Temp/ °C	Time	Conversion/ %
5	1 M	8	2	CD_3OD	rt	0.25 h	15
						0.5 h	38
						1 h	59
5	2 M	8	2	CD_3OD	rt	0.25 h	50
						0.5 h	90
						1 h	96
5	4 M	8	2	CD_3OD	rt	0.25 h	100

Table 4.2 Study of the effects of iodide concentration on reaction efficiency

To examine any inhibitory effect of iodine (a by-product of the reaction) on the reduction process, **Entry 10** (**Table 4.1**) was repeated with 6 equivalents of iodine also present. This reaction also resulted in 100% conversion to amine after 1 h. This result demonstrates that the formation of iodine during the reaction does not influence the transformation.

The possibility of carrying out the reduction using different acids of varying strengths was also investigated. The results are summarized in **Table 4.3**.

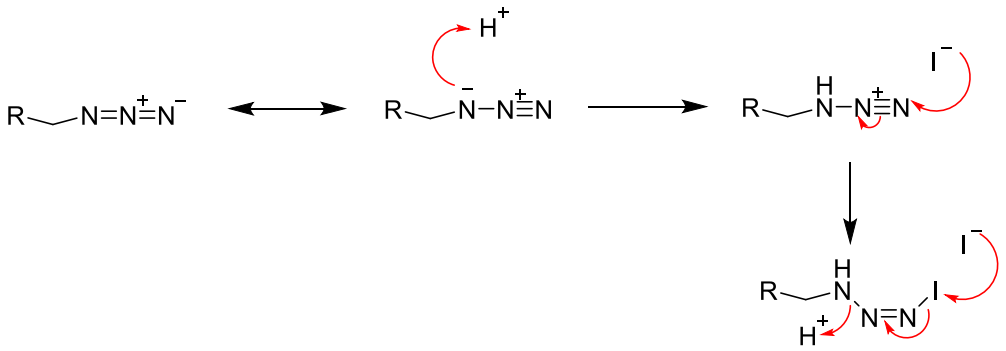


4.2a **4.2b**

Acids	^{1}H-NMR conversion/ %	pKa of acid
Amberlite (IR-120 H^+ form)	100	-
HCl	100	-8.0
TFA	54	-0.25
AcOH	-	4.76

Table 4.3 Variation of acid used for the azide reduction

The use of the strong acid HCl also caused complete conversion to the desired amine. However, weak acids such as trifluoroacetic acid and acetic acid diminished the conversion; trifluoroacetic acid gave only 54% conversion and no reaction was observed when AcOH was used as the proton source. These results demonstrate that the pKa of the acid plays an important role in the transformation of the azide to the amine; the efficiency of the reduction was significantly reduced using acids with higher pKa (e.g. AcOH, pKa 4.76), which suggests protonation of the nitrogen is required before iodide attack as shown in **Scheme 4.2**.



Scheme 4.2 Proposed mechanism for the reduction of azides to amines.

Amberlite IR 120 (H^+ form) was used as the source of acid in all subsequent reactions. As Amberlite can be recycled, the reaction efficiency was also tested with recycled Amberlite. In this process, **Entry 12** (**Table 4.1**) was repeated three times using the same Amberlite resin, which was regenerated after each reaction using the standard method (i.e. using 1 M aqueous HCl). As can be seen in the **Table 4.4**, 80% regeneration efficiency was observed.

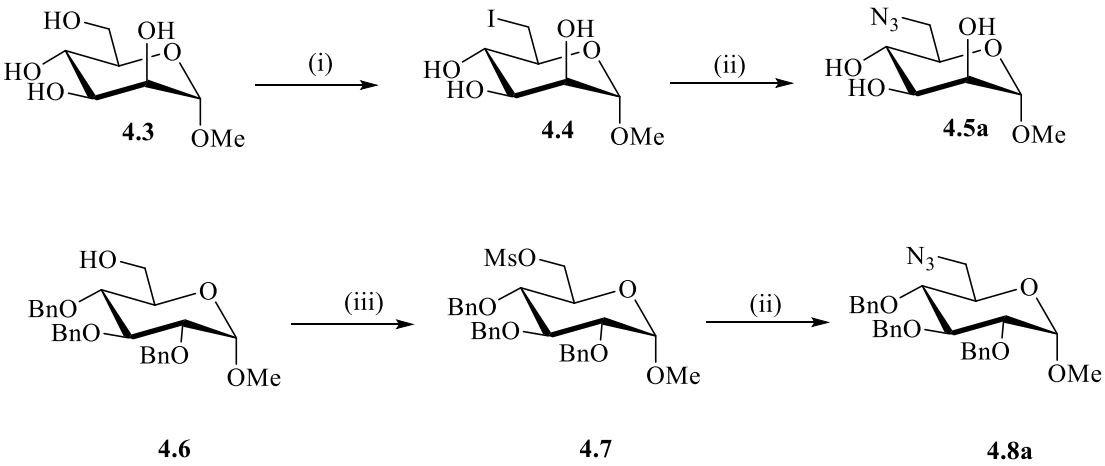
Recycle number	NaI/ Equiv.	Acid/ equiv.	Solvent	Temp/ °C	Time	1H-NMR conversion/ %
1	4	2	CH_3OH	40	0.25 h	100
2	4	2	CH_3OH	40	0.25 h	80
3	4	2	CH_3OH	40	0.25 h	80

Table 4.4 Study of the effect on reaction efficiency of Amberlite IR 120 (H^+ form) re-cycling

Having optimized the reaction conditions, the procedure was then applied to a variety of organoazides bearing different function groups. The azides were synthesised either from the corresponding alcohols or halides.

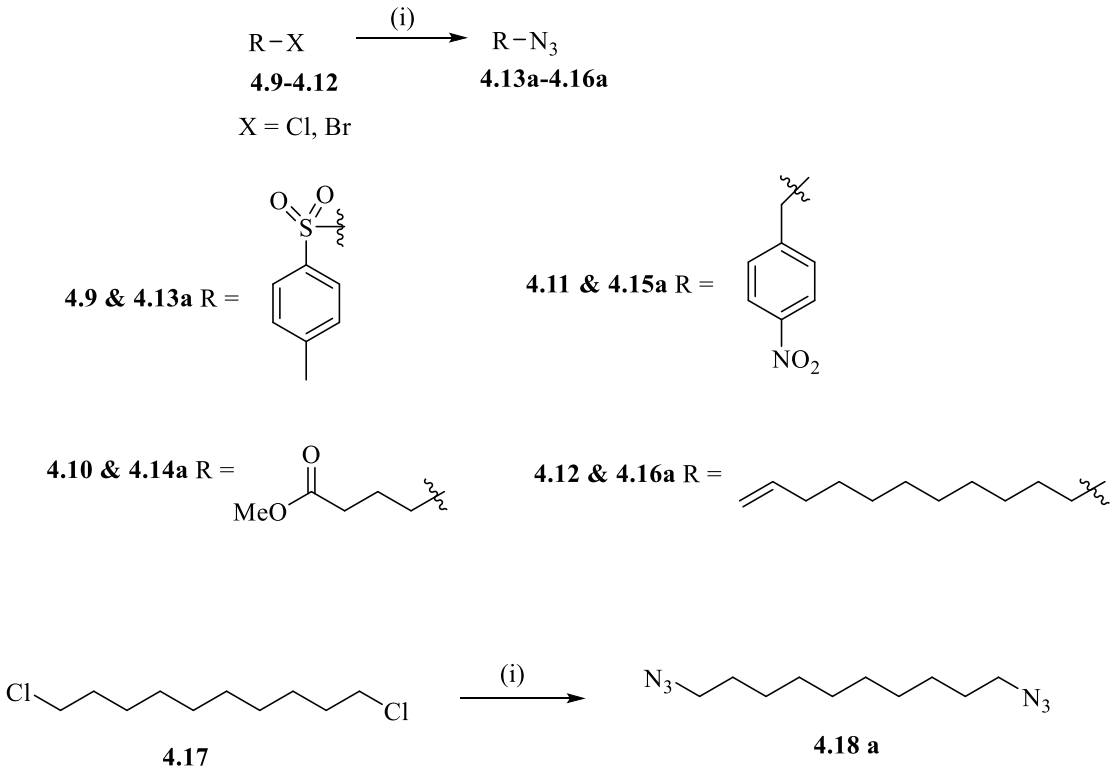
4.3 Synthesis of azides for reduction.

The substrates **4.2a, 4.19a** and **4.20a** (**Table 4.5**) were synthesised as described in Chapters 2 and 3. The other substrates were synthesised as shown in **Scheme 4.3** and **Scheme 4.4**.



Scheme 4.3 (i) PPh_3, I_2, Imidazole, THF, 50 °C, 16 h, 74 %; (ii) NaN_3, DMF, 50 °C, 16 h, **4.5a** – 74 %; **4.8a** – 95 % (iii) MsCl, Et_3N, DCM, 2 h.

The azides **4.5a** and **4.8a** were synthesised in two steps; firstly, primary alcohols **4.3** was iodinated with PPh_3, I_2, and imidazole using the Appel reaction, to afford iodides **4.4**. Primary alcohol of **4.6** was mesylated using methanesulfonyl chloride and triethylamine yielded mesylate **4.7**. The compound **4.4** and **4.7** were then converted to azides **4.5a** and **4.8a** using nucleophilic substitution with NaN_3. Similarly, azides **4.13a-4.16a** and **4.18a** were also synthesized by nucleophilic substitution using NaN_3 and the commercially available halides **4.9-4.12** and **4.17** (**Scheme 4.4**).



Scheme 4.4 (i) NaN_3, DMF, 50 °C, 16 h, **4.13a** – 68 %; **4.14a** – 70 %; **4.15a** – 67 %; **4.16a** – 71 %; **4.18a** – 80 %.

4.4 Reduction of azides to primary amines with different functional groups

From the optimization of the reaction discussed above, the NaI/Amberlite IR 120 (H^+ form) procedure on a rotary evaporator was the most efficient method for the selective transformation of azides to primary amines. With these conditions, the scope of the reduction was studied with several azides comprising other functional groups, such as benzyl ethers, alkenes, glycosides and nucleoside glycosidic linkages.

As can be seen from **Table 4.5**, ten azides with different functionality underwent smooth reduction using 4 equivalents of iodide and 2 equivalents of acid at 40 °C at a pressure of 200 mbar. MeOH was used as a solvent for the polar azides, and a mixture

of MeOH/$CHCl_3$ was used for less polar compounds due to poor solubility of these azides in MeOH.

The reaction products were purified by ion exchange chromatography. For the purification method, an excess of Amberlite was added after the reaction was completed, then the Amberlite was washed with water to remove all other salts and impurities. Finally, a 2.5 M ammonia solution in MeOH was used to elute the desired product, which in all cases was isolated in excellent yield. The products could also be purified by silica-gel flash column chromatography following the removal of resin by filtration.

The scope of the reduction was only studied for monosaccharides. This reduction required strong acidic conditions, and therefore this method could be problematic for oligosaccharides, particularly with glycans containing furanosidic, fucosidic, or rhamnosidic bonds, which could be hydrolysed under acidic conditions.

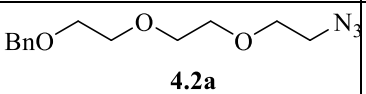
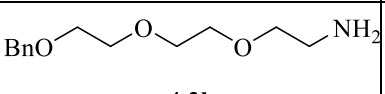
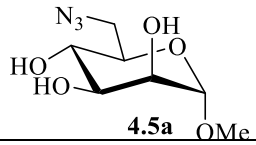
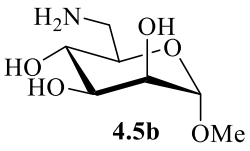
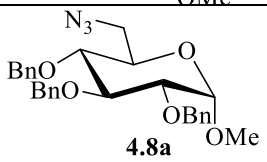
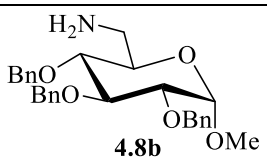
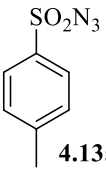
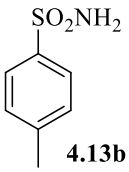
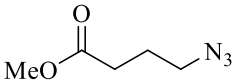
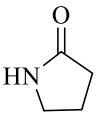
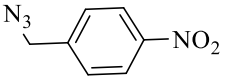
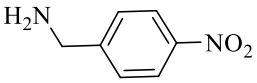
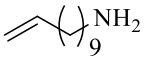
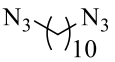
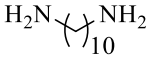
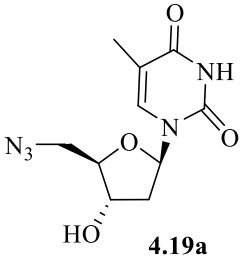
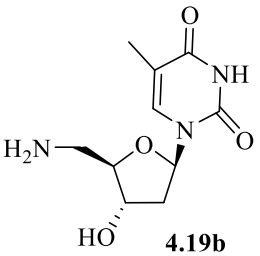
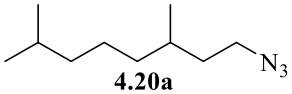
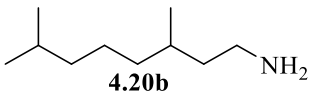
Entry	Starting material	Product	Solvent	Yield (%)
1	 **4.2a**	 **4.2b**	MeOH	89
2	 **4.5a**	 **4.5b**	MeOH	91
3	 **4.8a**	 **4.8b**	$CHCl_3$/MeOH 3:2	93
4	 **4.13a**	 **4.13b**	$CHCl_3$/MeOH 3:2	95
5	 **4.14a**	 **4.14b**	$CHCl_3$/MeOH 3:2	quant.
6	 **4.15a**	 **4.15b**	$CHCl_3$/MeOH 3:2	quant.
7	 **4.16a**	 **4.16b**	$CHCl_3$/MeOH 3:2	87
8	 **4.18a**	 **4.18b**	$CHCl_3$/MeOH 3:2	92
9	 **4.19a**	 **4.19b**	MeOH	93
10	 **4.20a**	 **4.20b**	$CHCl_3$/MeOH 3:2	85

Table 4.5 Reduction of azides into primary amines by NaI/Amberlite IR120 (H^+ form)

4.5 Conclusions

A simple, efficient, and mild reduction method for the conversion of azides into amines was developed, which is low cost, is easily removed from the reaction by filtration, and displays high chemoselectivity. The reduction is highly efficient when performed at 40 °C, 200 mbar with four equivalents of iodide and two equivalents of acid. In addition, optimization of the iodide concentration revealed that the efficiency of the reaction depends on the iodide concentration. Complete conversion to product was observed when the reaction was performed with an iodide concentration of 4 M and two equivalents of Amberlite IR120 (H^+ form). Other strong acids could also be used for the reduction. However, the process is simple, rapid and clean when Amberlite ion exchange resin is used as a proton source. The resin can be recycled effectively, and also used for the purification of the polar amine products. This new reduction method has good functional group tolerance; for example alkenes, benzyl ethers, glycosides, sulfonyl groups, and nitro groups are all unaffected by the process.

Chapter 5 Experimental section

5.1 General chemical experimental

Melting points were recorded on an Electrothermal® melting point apparatus. Proton and carbon nuclear magnetic resonance (δ_H, δ_C) spectra were recorded on Bruker AV 400 (400 MHz), or Bruker AV 500 (500 MHz) spectrometers. All chemical shifts are quoted on the δ-scale in ppm using residual solvent as an internal standard. High-resolution mass spectra were recorded on a Bruker FT-ICR electrospray ionisation mass spectrometer, using either electrospray ionisation techniques as stated. *M/z* values are reported in Daltons and are followed by their percentage abundance in parentheses. Optical rotations ($[\alpha]_D^T$ in $deg \cdot mL \cdot g^{-1} \cdot dm^{-1}$) were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g / 100 mL. Thin Layer Chromatography (t.l.c.) was carried out on Merck Silica gel $60F_{254}$ aluminium-backed plates. Visualisation of the plates was achieved using a u.v. lamp (λ_{max} = 254 or 365 nm), and/or ammonium molybdate (5% in 2 M sulfuric acid), or sulfuric acid (5% in ethanol). Infrared spectra were recorded on a Bruker FTIR spectrometer with Alpha's Platinum ATR single reflection diamond where the neat samples were recorded. Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Reverse phase high performance liquid chromatography (RP-HPLC) was performed on a Dionex P680 HPLC instrument with a Phenomenex Luna C 18(2) 100 A column (5 µm, 10 x 250 mm) at 15 °C. The column was eluted with a gradient of $MeCN/H_2O$ at a flow rate of 1 $mLmin^{-1}$. Alcohol-free dichloromethane was dried on an alumina column. Anhydrous DMF, pyridine, methanol and toluene were purchased from Sigma Aldrich. 'Petrol' refers to the

fraction of light petrol ether boiling in the range of 40-60 °C. Elemental analysis was performed by Campbell microanalytical laboratory, University of Otago.

5.2 Experimental for chapter 2

General Procedures

General Procedure A

Tert-butyl alcohol (1.5 equiv) was added dropwise to a stirred solution of chlorosulfonyl isocyanate (1 equiv) in dry DCM (15 mL) at 0 ˚C under nitrogen. The solution was stirred for a further 30 minutes at 0 ˚C before a solution of the amine (1 equiv) and dry triethylamine (1.5 equiv) in dry DCM (15 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature, and then stirred for 16 hours. The reaction mixture was then diluted with DCM (20 mL), washed with saturated aqueous $NaHCO_3$ (3 x 20 mL) and brine (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue that was then purified by flash chromatography.

General Procedure B:

Trifluoroacetic acid (4.5 equiv) was added to a solution of sulfamide (1 equiv) in DCM (25 mL). The solution was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo*, and the residue then purified by flash chromatography.

General Procedure C:

2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranose **2.7** (1 equiv), and the sulfamide (1.2 equiv), and crushed activated 3Å molecular sieves (~ 400 mg) were stirred at room temperature in dry DCM (15 mL) under nitrogen. TMSOTf (1 equiv) was added dropwise, and the mixture was then stirred for 16 hours. The reaction was neutralized by the dropwise addition of excess triethylamine (0.3 mL). The reaction mixture was then filtered through Celite®, eluting with ethyl acetate, and concentrated *in vacuo* to give a residue which was purified by flash chromatography.

General Procedure D:

Methanesulfonyl chloride (1.5 equiv) was added dropwise to a stirred solution of alcohol (1 equiv) and Et_3N (1.5 equiv) in anhydrous DCM (30 mL) at 0 ˚C under nitrogen. The reaction was allowed to warm to room temperature, and stirred for 2 hours. The reaction mixture was poured into methanol (10 mL), and concentrated *in vacuo*. The reaction mixture was then diluted with diethyl ether (20 mL), washed with water (3 x 20 mL) and brine (3 x 20 mL). The combined organic extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in DMF (25 mL), sodium azide (3 equiv.) was added, and the mixture was stirred at 60 ˚C for 16 hours. The reaction mixture was concentrated *in vacuo*, and The reaction mixture was then diluted with diethyl ether (50 mL), washed with water (3 x 20 mL) and brine (3 x 30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo,* which was purified by flash chromatography.

General Procedure E:

Triphenylphosphine (2 equiv) and water (1.5 equiv) were added to a stirred solution of azide (1 equiv) in THF (25 mL) under nitrogen. The reaction was stirred under nitrogen for 16 hours. The reaction mixture was concentrated *in vacuo*, which was then purified by flash chromatography.

General Procedure F:

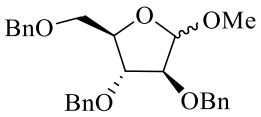
10 % Activated Pd-C (20 mg) was added to a solution of the protected glycosyl sulfamide (0.1 mmol) in methanol (5 mL). The flask was evacuated and purged with nitrogen five times, before it was placed under an atmosphere of hydrogen. The solution was stirred for 16 hours at room temperature. The reaction mixture was filtered through Celite® (eluting with methanol 20 mL), and concentrated *in vacuo* to give a residue which was purified by flash column chromatography.

General Procedure G:

Sodium hydride (60 % dispersion in mineral oil, 0.5 equiv) was added portionwise to a solution of triethyleneglycol (1 equiv) in THF (50 mL) under nitrogen. The reaction was stirred for 1 hour and then cooled to 0 ˚C. Benzyl bromide (0.5 equiv) was then added dropwise, and the reaction mixture was warmed to room temperature and then stirred for 16 hours. The reaction mixture was cooled in an ice bath quenched by the addition of methanol (20 mL), and then concentrated *in vacuo*. The residue was dissolved in DCM (30 mL), and washed with water (30 mL). The combined organic

extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*, which was purified by flash chromatography.

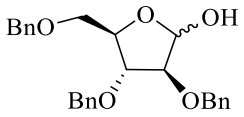
Methyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside 2.7[92]



Acetyl chloride (3.08 mL, 43 mmol) was added dropwise to a solution of D-arabinose (5.0 g, 33 mmol) in methanol (100 mL) under nitrogen. The reaction was stirred for 3 hours at room temperature. After this time, t.l.c. (DCM: MeOH, 4:1) indicated the formation of two products, a major product (methyl α,β-D-arabinofuranoside, R_f 0.5) and the complete consumption of starting material (R_f 0.2). The reaction mixture was neutralized by adding solid K_2CO_3 (~7 g), filtered, concentrated *in vacuo*, and the residue was co-evaporated with toluene (3 x 50 mL) to afford a crude mixture of methyl α,β-D-arabinofuranoside and methyl α,β-D-arabinopyranoside as a brown oil which was used in the next step without further purification. Sodium hydride (60 % dispersion in mineral oil, 8.2 g, 205 mmol) was added dropwise to a solution of the mixture produced above (5.6 g, 34 mmol) in DMF (60 mL) under nitrogen. The reaction was stirred for 1 hour and then cooled to 0 °C. Benzyl bromide (24.3 mL, 205 mmol) was then added dropwise. The reaction mixture was warmed to room temperature and then stirred for 16 hours. After this time, t.l.c. (petrol: ethyl acetate, 7:1) indicated the formation of a major product (R_f 0.2), and the complete consumption of starting material (R_f 0.0). The reaction was cooled in an ice bath, quenched by the addition of methanol (90 mL), and then concentrated *in vacuo*. The residue was dissolved in diethyl ether (50 mL), and washed with brine (3 x 50 mL).

The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil, which was purified by flash chromatography (petrol: ethyl acetate, 7:1) to afford methyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside **2.7** (7.7 g, 54 %, α:β, 3:1) as a clear oil. δ_H (500 Hz, $CDCl_3$) α-anomer: 3.42 (3H, s, OCH_3), 3.64 (2H, at, *J* 4.8 Hz, H-5, H-5'), 3.94 (1H, dd, $J_{3,4}$ 6.2 Hz, $J_{2,3}$ 2.8 Hz, H-3), 4.03 (1H, m, H-2), 4.25 (1H, td, $J_{4,5}$ 5.4 Hz, $J_{4,5'}$ 5.4 Hz, $J_{3,4}$ 4.8 Hz, H-4), 4.56-4.59 (6H, m, $PhCH_2$), 4.98 (1H, s, H-1), 7.26-7.39 (15H, m, Ar-H); β anomer: 3.35 (3H, s, OCH_3), 3.56 (1H, dd, $J_{5,5'}$ 8.9 Hz, $J_{4,5}$ 6.0 Hz, H-5), 3.61 (1H, d, $J_{4,5'}$ 5.4 Hz, H-5'), 4.08-4.12 (1H, m, H-4), 4.13-4.14 (1H, m, H-2), 4.15-4.17 (1H, m, H-3), 4.51 (5H, ABq, *J* 9.8 Hz, $PhCH_2$) 4.62-4.66 (1H, m, $PhCH_2$), 4.76 (1H, d, *J* 4.2 Hz, H-1), 7.26-7.39 (15H, m, Ar-H); HRMS (ESI) calculated for $C_{27}H_{30}NaO_5$: 457.1991 Found: 457.1984 (MNa^+).

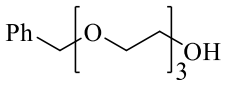
2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranose 2.6[93]



Methyl 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranoside **2.7** (7.7 g, 18 mmol) was dissolved in a mixture of water and acetic acid (100 mL, 1:4, v/v), and then stirred at 115 ˚ C for 2 days. After this time, t.l.c. (petrol: ethyl acetate 3:1) indicated the formation of a single product (R_f 0.2), and the complete consumption of starting material (R_f 0.6). The reaction was quenched by the addition of ice water (100 mL), and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow

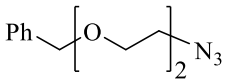
oil, which was purified by flash chromatography (petrol: ethyl acetate, 3:1) to afford 2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranose **2.6** (4.8 g, 64 %, α:β, 1:1) as a white crystalline solid. δ_H (500 MHz, $CDCl_3$) α anomer: 3.52-3.62 (2H, m, H-5, H-5'), 3.93-3.95 (1H, m, H-3), 3.98-3.99 (1H, m, H-2), 4.46-4.48 (1H, m, H-4), 4.51-4.67 (6H, m, $PhCH_2$), 5.40 (1H, s, H-1), 7.26-7.37 (15H, m, Ar-H); β anomer: 3.52-3.62 (2H, m, H-5, H-5'), 4.02 (1H, d, *J* 4.5 Hz, H-2), 4.09 (1H, aq, *J* 4.3 Hz, H-4), 4.17 (1H, t, *J* 4.5 Hz, H-3), 5.33 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 4.51-4.67 (6H, m, $PhCH_2$), 7.26-7.37 (15H, m, Ar-H); HRMS (ESI) calculated for $C_{26}H_{28}NaO_5$: 443.1834. Found: 443.1851 (MNa^+).

2-(2-(2-(Benzyloxy)ethoxy)ethoxy)ethanol 2.11b[137]



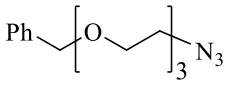
General procedure G, using triethyleneglycol **2.10b**, and purification by flash chromatography (petrol: ethyl acetate, 2:1, R_f 0.2), afforded benzyl ether **2.11b** (6.56 g, 36 %) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$)[137] 2.75 (1H, s, OH), 3.58-3.71 (12H, m, 6 x OCH_2), 4.55 (2H, s, $PhCH_2$), 7.26-7.33 (5H, m, Ar-H); HRMS (ESI) calculated for $C_{13}H_{20}NaO_4$: 263.1259 Found: 263.1250 (MNa^+).

((2-(2-Azidoethoxy)ethoxy)methyl)benzene 2.12a



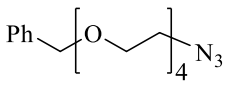
General procedure D, using alcohol **2.11a**, and purification by flash chromatography (petrol: ethyl acetate, 1:1, R_f 0.8), afforded azide **2.12a** (0.45 g, 94 %) as a clear oil. υ_{max} (neat) 2099 (s, N_3) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.39 (2H, t, *J* 5.0 Hz, CH_2N_3), 3.64-3.69 (6H, m, 3 x CH_2), 4.58 (2H, s, $PhCH_2$), 7.27-7.35 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 50.7 (t, CH_2N_3), 69.4, 70.0, 70.7 (3 x t, 3 x CH_2), 73.3 (t, $PhCH_2$), 127.6, 127.7, 128.4 (3 x d, 5 x Ar(C)H), 138.1 (s, Ar-C); HRMS (ESI) calculated for $C_{11}H_{15}N_3NaO_2$ 244.1062. Found 244.1074 (MNa^+).

((2-(2-(2-Azidoethoxy)ethoxy)ethoxy)methyl)benzene 2.12b



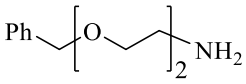
General procedure D, using alcohol **2.11b**, and purification by flash chromatography (petrol: ethyl acetate, 1:1, R_f 0.4), afforded azide **2.12b** (4.38 g, 98 %) as a clear oil. υ_{max} (neat) 2097 (s, N_3) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.36 (2H, t, *J* 4.0 Hz, CH_2N_3), 3.63-3.68 (10H, m, 5 x CH_2), 4.56 (2H, s, $PhCH_2$), 7.26-7.34 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 50.6 (t, CH_2N_3), 69.4, 70.0, 70.6, (3 x t, 5 x CH_2), 73.2 (t, $PhCH_2$), 127.5, 127.7, 128.3 (3 x d, 5 x Ar(C)H), 138.2 (s, Ar-C); HRMS (ESI) calculated for $C_{13}H_{19}N_3NaO_3$ 288.1324. Found 288.1319 (MNa^+).

((2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethoxy)methyl)benzene 2.12c



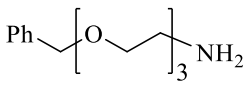
General procedure D, using alcohol **2.11c,** and purification by flash chromatography (petrol: ethyl acetate, 1:1, R_f 0.5), afforded azide **2.12c** (0.54 g, 91 %) as a clear oil. υ_{max} (neat) 2097 (s, N_3) cm-1; δ_H (500 MHz, $CDCl_3$) 3.37 (2H, t, *J* 5.0 Hz, CH_2N_3), 3.63-3.66 (14H, m, 7 x CH_2), 4.56 (2H, s, $PhCH_2$), 7.26-7.33 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 50.7 (t, CH_2N_3), 69.5, 70.1, 70.5, 70.6, 70.7, 70.8, 70.9 (7 x t, 7 x CH_2), 73.3 (t, Ph-CH_2), 127.9, 128.3, 128.6 (3 x d, 3 x Ar(C)H), 138.3 (s, Ar-C); HRMS (ESI) calculated for $C_{115}H_{24}N_3O_4$ 310.1767. Found 310.1764 (MH^+).

2-(2-(Benzyloxy)ethoxy)ethanamine 2.13a



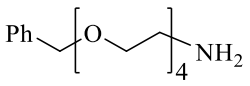
General procedure E, using azide **2.12a**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.1), afforded amine **2.13a** (0.25 g, 71 %) as a clear oil. υ_{max} (neat) 3260 (w, NH_2) cm^{-1} ; δ_H (500 MHz, $CDCl_3$) 2.09 (2H, s, NH_2), 2.85 (2H, t, *J* 5.0 Hz, CH_2N), 3.50 (2H, t, *J* 5.0 Hz, OCH_2), 3.62-3.64 (4H, m, 2 x CH_2) 4.56 (2H, s, $PhCH_2$), 7.25-7.34 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 41.3 (t, CH_2N), 69.4, 70.3 (2 x t, 2 x CH_2), 72.3 (t, OCH_2), 73.3 (t, Ph-CH_2), 127.7, 127.8, 128.3, 128.3, 128.4 (5 x d, 5 x Ar(C)H), 138.0 (s, Ar-C); HRMS (ESI) calculated for $C_{11}H_{18}NO_2$ 196.1338. Found 196.1336 (MH^+).

2-(2-(2-(Benzyloxy)ethoxy)ethoxy)ethanamine 2.13b



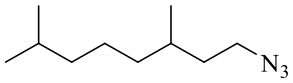
General procedure E, using azide **2.12b**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.1), afforded amine **2.13b** (3.10 g, 80 %) as a clear oil. υ_{max} (neat) 3260 (w, NH_2) cm^{-1} ; δ_H (400 MHz, $CDCl_3$)[41] 1.81 (2H, s, NH_2), 2.84 (2H, t, *J* 6.0 Hz, CH_2N), 3.41 (2H, t, *J* 8.0 Hz, OCH_2), 3.61-3.67 (8H, m, 4 x CH_2) 4.55 (2H, s, $PhCH_2$), 7.24-7.32 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 41.7 (t, CH_2N), 69.4, 70.3, 70.6 (3 x t, 5 x CH_2), 73.2 (t, $PhCH_2$), 127.6, 127.7, 128.3 (3 x d, 5 x Ar(C)H), 138.2 (s, Ar-C); HRMS (ESI) calculated for $C_{13}H_{21}NNaO_3$ 262.1419. Found 262.1414 (MNa^+).

2-(2-(2-(2-(Benzyloxy)ethoxy)ethoxy)ethoxy)ethanamine 2.13c



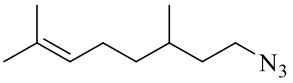
General procedure E, using azide **2.12c**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.1), afforded amine **2.13c** (0.23 g, 67 %) as a clear oil. υ_{max} (neat) 3264 (w, NH_2) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.23 (2H, s, NH_2), 2.79 (2H, t, *J* 5.0 Hz, CH_2N), 3.52 (2H, t, *J* 5.0 Hz, OCH_2), 3.62-3.68 (12H, m, 6 x CH_2) 4.56 (2H, s, $PhCH_2$), 7.25-7.34 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 40.9 (t, CH_2N), 69.4, 69.6, 70.3, 70.4, 70.4, 70.6, 71.0 (7 x t, 7 x CH_2), 73.2 (t, $PhCH_2$), 127.8, 128.0, 128.3 (3 x d, 5 x Ar(C)H, 137.8 (s, Ar-C); HRMS (ESI) calculated for $C_{15}H_{26}NO_4$ 284.1862. Found 284.1863 (MH^+).

1-Azido-3,7-dimethyloctane 2.15a



General procedure D, using alcohol **2.14a**, and purification by flash chromatography (petrol, R_f 0.9), afforded azide **2.15a** (4.26 g, 75 %) as a clear oil. υ_{max} (KBr) 2096 (s, N_3) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.85-0.89 (9H, m, 3 x CH_3), 1.11-1.15 (2H, m, CH_2), 1.21-1.31 (2H, m, CH_2), 1.35-1.41 (2H, m, CH_2), 1.48-1.50 (2H, m, CH_2), 1.51-1.64 (2H, m, 2 x CH), 3.23-3.29 (2H, m, CH_2N_3); δ_C (125 MHz, $CDCl_3$) 19.3, 22.6, 22.7 (3 x q, 3 x CH_3), 24.6 (t, CH_2), 27.9, 30.3 (2 x d, 2 x CH), 35.7, 37.0, 39.2 (3 x t, 3 x CH_2), 49.5 (t, CH_2N_3); Micro elemental analysis requires for $C_{10}H_{21}N_3$: C 65.53 %, H 11.55 %, 22.93 %; Found C 65.74 %, H 11.54 %, 22.72 %.

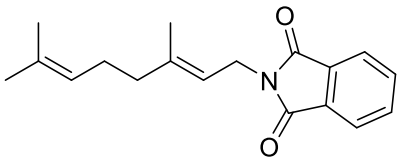
8-Azido-2,6-dimethyloct-2-ene 2.15b



General procedure D, using 3,7-dimethyloct-6-en-1-ol **2.14b**, and purification by flash chromatography (petrol; R_f 0.5), afforded azide **2.15b** (1.1 g, 56 %) as a clear oil. υ_{max} (neat) 2089 (s, C-N_3) cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 8.0 Hz, $CHCH_3$), 1.18-1.43 (4H, m, 2 x CH_2), 1.55-1.69 (8H, m, CH_2, 2 x CH_3), 1.96- 2.01 (2H, m, =CHC$\underline{H}_2$), 3.28 (2H, m, CH_2N_3), 5.09 (1H, t, *J* 8.0 Hz, =CH); δ_C (125 MHz, $CDCl_3$) 17.6, 19.1, 25.3 (3 x q, 3 x CH_3), 25.6 (t, =CH$\underline{C}H_2$), 29.9, 35.6, 36.8 (3 x t, 3 x CH_2), 49.5 (t, CH_2N_3), 124.4 (d, =CH), 131.4 (s, $C(CH_3)_2$). Micro elemental analysis

requires for $C_{10}H_{19}N_3$ C 66.26 %, H 10.56 %, 23.18 %; found C 65.59 %, H 10.43 %, 21.59 %.

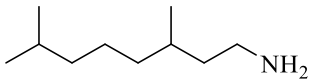
(*E*)-3,7-dimethylocta-2,6-dien-1-phthalimide 2.15c[138]



Methanesulfonylchloride (1.31 mL, 17 mmol) was added dropwise to a stirred solution of (*E*)-3,7-dimethylocta-2,6-dien-1-ol **2.14c** (2 mL, 11 mmol) and Et_3N (2.35 mL, 17 mmol) in anhydrous DCM (30 mL) at 0 ˚C under nitrogen. The reaction was allowed to warm n to room temperature and stirred for 2 hours. After this time, t.l.c (Petrol: Ethyl acetate, 1:1) indicated the formation of a single product (R_f 0.9), and complete consumption of starting material (R_f 0.6). The reaction mixture was poured into methanol (20 mL), and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was dissolved in DMF (30 mL) and potassium phthalimide (4.2 g, 34 mmol, 2 equiv.) was added. The resulting solution was stirred at 70 °C for 16 hours. After this time, t.l.c (Petrol: Ethyl acetate, 3:1) indicated the formation of a single product (R_f 0.6), and complete consumption of starting material (R_f 0.4). The reaction mixture was cooled, poured into water (30 mL), and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo* to afford a yellow solid, which was purified by flash chromatography (Petrol: Ethyl acetate, 3:1) to afford phthalimide **2.15c** (1.94 g, 60 %) as pale yellow solid. m.p 62-65 °C (EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 1.47,

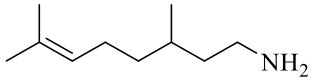
1.53, 1.75 (9H, 3 x s, 3 x CH_3), 1.93-1.99 (4H, m, 2 x CH_2), 4.17 (2H, d, *J* 8 Hz, CH_2N), 4.95, 5.20 (2H, 2 x t, *J* 8 Hz, C=CH), 7.60,7.72 (4H, 2 x d, $J_{1,2}$ 4 Hz, $J_{1,3}$ 8 Hz, Ar-H); HRMS (ESI) calculated for $C_{18}H_{21}NNaO_2$ ($M+Na^+$) 306.1470. Found 306.1458.

3,7-Dimethyl-1-octanamine 2.16a



General procedure E, using azide **2.15a**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.2), afforded amine **2.16a** (1.6 g, 63 %) as a clear oil. υ_{max} (neat) 3260 (w, C-NH_2) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.81-0.83 (9H, m, 3 x CH_3), 1.10-1.27 (8H, m, 4 x CH_2), 1.40-1.49 (2H, m, 2 x CH), 1.89 (s,NH_2), 2.69 (2H, m, CH_2N); δ_C (125 MHz, $CDCl_3$) 19.6, 22.6, 22.7 (3 x q, 3 x CH_3), 24.6 (t, CH_2), 27.9, 30.4 (2 x d, 2 x CH), 37.3, 39.2, 39.9 (3 x t, 3 x CH_2), 40.7 (t, CH_2N); HRMS (ESI) calculated for $C_{10}H_{24}N$: 158.1909 . Found: 158.1906 (MH^+).

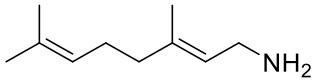
3,7-Dimethyloct-6-en-1-amine 2.16b



General procedure E, using azide **2.15b**, and purification by the flash chromatography (DCM: MeOH, 19:1; R_f 0.0), afforded amine **2.16b** (0.66 g, 71 %) as a yellow oil. υ_{max} (neat) 3260 (w, C-NH_2) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 4.0 Hz, CH_3),

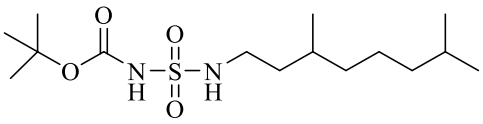
1.15, 1.30, 1.50 (6H, m, 3 x CH_2), 1.60, 1.68 (6H, 2 x s, 2 x CH_3), 1.79 (2H, s, NH_2), 1.97 (2H, m, =CHC$\underline{H}_2$), 2.72 (2H, m, CH_2N_3), 5.09 (1H, t, *J* 8.0 Hz, =CH); δ_C (125 MHz, $CDCl_3$) 17.6, 19.5, 25.4 (3 X q, 3 X CH_3), 25.6 (t, =CH$\underline{C}H_2$), 30.1, 37.1, 39.8 (3 x t, 3 x CH_2), 40.7 (t, CH_2N_3), 124.7 (d, =CH), 131.1 (s, $\underline{C}(CH_3)_2$). HRMS (ESI) calculated for $C_{10}H_{22}N$ ($M+H^+$) 156.1752. Found 156.1748.

(*E*)-3,7-dimethylocta-2,6-dien-1-amine 2.16c[138]



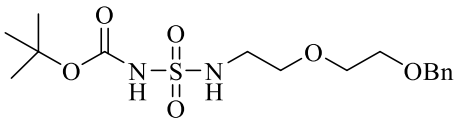
$N_2H_4.H_2O$ (0.7 mL, 14 mmol, 2 equiv.) was added to phthalimide **2.15c** (1.9 g , 7 mmol) in ethanol (60 mL) and then the mixture was refluxed for 16 hours. After this time, t.l.c (DCM: MeOH 19:1) indicated the formation of a single product (R_f 0.2), and complete consumption of starting material (R_f 0.9). The reaction mixture was cooled, and was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was then purified by flash chromatography (DCM: MeOH, 19:1) to afford amine **2.16c** (0.45 g, 43 %) as yellow oil. δ_H (400 MHz, $CDCl_3$)[138] 1.58, 1.61, 1.66 (9H, 3 x s, 3 x CH_3), 2.03-2.07 (4H, m, 2 x CH_2), 3.26 (2H, m, CH_2N), 5.07, 5.24 (2H, 2 x t, *J* 8.0 Hz, 2 x =CH). HRMS (ESI) calculated for $C_{10}H_{20}N$ ($M+H^+$) 154.1596. Found 154.1588.

***tert*-Butyl *N*-3,7-dimethyloctylsulfamoylcarbamate 2.18j**



General procedure A, using amine **2.16a**, and purification by flash chromatography (DCM, R_f 0.4), afforded sulfamoylcarbamate **2.18j** (646 mg, 73 %) as a colourless solid; υ_{max} (neat) 3250 (N-H), 1697 (s, C=O), 1345 (s, S=O), 1137 (s, S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.85-0.88 (9H, m, 3 x CH_3), 1.11-1.15 (2H, m, CH_2), 1.21-1.31 (2H, m, CH_2), 1.35-1.41 (2H, m, CH_2), 1.49 (9H, s, 3 x CH_3), 1.51-1.64 (4H, m, 2 x CH, CH_2), 3.04-3.11 (2H, m, $C\underline{H}_2NHSO_2$), 5.19 (1H, br. s, $CH_2N\underline{H}SO_2$); δ_C (125 MHz, $CDCl_3$) 19.2, 22.6, 22.7 (3 x q, 3 x CH_3), 24.5 (t, CH_2), 27.9 (d, CH), 28.0 (q, ($C(CH_3)_3$), 30.2 (d, CH), 36.1, 37.0, 39.2 (3 x t, 3 x CH_2), 42.0 (t, $NHCH_2$), 83.7 (s, $C(CH_3)_3$), 150.3 (s, C=O); HRMS (ESI) calculated for $C_{15}H_{32}N_2NaO_4S$: 359.1980. Found: 359.1977 (MNa^+).

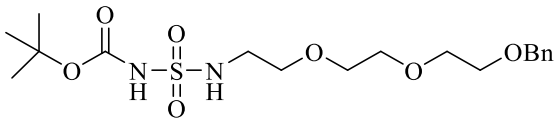
***T*ert-butyl *N*-2-(2-(Benzyloxy)ethoxy)ethylsulfamoylcarbamate 2.18k**



General procedure A, using amine **2.13a**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.5), afforded sulfamoylcarbamate **2.18k** (0.36 g, 93 %) as a white solid. m.p. 68-70 °C (petrol/ EtOAc); υ_{max} (neat) 1708 (s, C=O), 1351 (s, S=O), 1139 (s, S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.46-1.48 (9H, s, $C(C\underline{H}_3)_3$), 3.29 (2H, q, *J* 5.5 Hz, CH_2NH), 3.61-3.64 (6H, m, 3 x CH_2), 4.57 (2H, s, $PhCH_2$), 5.63(1H, t, *J* 10

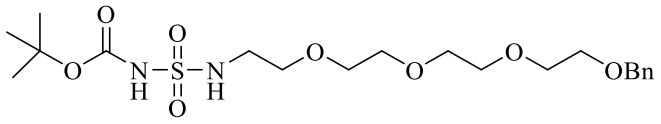
Hz, $CH_2N\underline{H}$), 7.26-7.35 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 27.9 (q, $C(\underline{C}H_3)_3$), 43.6 (t, $\underline{C}H_2NH$), 69.3, 70.2 (2 x t, 3 x CH_2), 73.3 (t, $PhCH_2$), 83.5 (s, $C(CH_3)_3$), 127.7, 127.9, 128.4 (3 x d, 3 x Ar(C)H), 138.0 (s, Ar-C), 150.4 (s, C=O); HRMS (ESI) calculated for $C_{16}H_{26}N_2NaO_6S$ 397.1409. Found 397.1410 (MNa^+).

***Tert*-butyl *N*-2-(2-(2-(Benzyloxy)ethoxy)ethoxy)ethylsulfamoylcarbamate 2.18l**



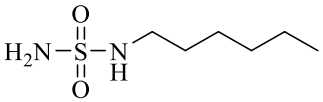
General procedure A, using amine **2.13b**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.4), afforded sulfamoylcarbamate **2.18l** (1.35 g, 39 %) as a clear oil. υ_{max} (neat) 1715 (s, C=O), 1350 (s, S=O), 1150 (s, S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$)[41] 1.44-1.47 (9H, s, $C(C\underline{H}_3)_3$), 3.27-3.30 (2H, m, $C\underline{H}_2NH$), 3.61-3.67 (10H, m, 5 x CH_2), 4.57 (2H, s, Ph-CH_2), 7.26-7.34 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 28.0 (q, $C(\underline{C}H_3)_3$), 43.6 (t, $\underline{C}H_2NH$), 69.3, 70.1, 70.6 (3 x t, 5 x CH_2), 73.2 (t, $PhCH_2$), 83.2 (s, $\underline{C}(CH_3)_3$), 127.6, 127.8, 128.3 (3 x d, 5 x Ar(C)H), 138.1 (s, Ar-C), 150.4 (s, C=O); HRMS (ESI) calculated for $C_{18}H_{30}N_2NaO_7S$ 441.1671. Found 441.1666 (MNa^+).

***Tert*-butyl*N*-2-(2-(2-(2(benzyloxy)ethoxy)ethoxy)ethoxy)ethylsulfamoylcarbamate 2.18m**



General procedure A, using amine **2.13c**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.3), afforded sulfamoylcarbamate **2.18m** (0.33 g, 91 %) as a clear oil. υ_{max} (neat) 1729 (s, C=O), 1350 (s, S=O), 1090 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, $C(\underline{C}H_3)_3$), 3.29 (2H, m, $C\underline{H}_2NH$), 3.59-3.68 (14H, m, 7 x CH_2), 4.57 (2H, s, $PhCH_2$), 7.25-7.34 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 28.1 (q, $C(\underline{C}H_3)_3$), 43.7 (t, $\underline{C}H_2NH$), 69.4, 70.1, 70.6 (3 x t, 7 x CH_2), 73.2 (t, $PhCH_2$), 83.2 (s, $\underline{C}(CH_3)_3$), 127.6, 127.8, 128.3 (3 x d, 3 x Ar(C)H, 138.2 (s, Ar-C), 150.5 (s, C=O); HRMS (ESI) calculated for $C_{20}H_{34}N_2NaO_8S$ 485.1934. Found 485.1921 (MNa^+).

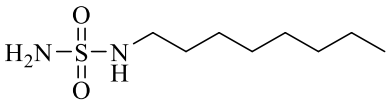
***N*-(Hexyl)sulfamide 2.19a**



General Procedure B, using sulfamoylcarbamate **2.18a**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.3), afforded sulfamide **2.19a** (280 mg, 86 %) as a white solid; m.p. 67-70 °C (DCM); υ_{max} (neat) 3331 (N-H), 3289 (N-H), 1357 (s, S=O), 1130 (s, S=O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.4 Hz, CH_3), 1.28-1.37

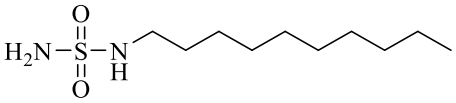
(6H, m, 3 x CH_2), 1.53-1.61 (2H, m, $NHCH_2C\underline{H}_2$), 3.13 (2H, t, *J* 7.2 Hz, $C\underline{H}_2NHSO_2$), 4.52 (2H, br s, NH_2); δ_C (100.5 MHz, $CDCl_3$) 13.9 (q, CH_3), 22.5, 26.3, 29.4, 31.3, (4 x t, 4 x CH_2), 43.7 (t, $\underline{C}H_2NH$); HRMS (ESI) calculated for $C_6H_{16}N_2NaO_2S$: 203.0830. Found: 203.0825 (MNa^+).

_N_-(Octyl)sulfamide 2.19b



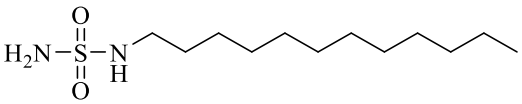
General Procedure B, with sulfamoylcarbamate **2.18b**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.3), afforded sulfamide **2.19b** (472 mg, 69 %) as a white solid; m.p. 82-85 °C (DCM); υ_{max} (neat) 3330 (N-H), 3283 (N-H), 1345 (s, S=O), 1135 (s, S=O); δ_H (400 MHz, DMSO) 0.85 (3H, t, *J* 6.8 Hz, $C\underline{H}_3$), 1.18-1.30 (10H, m, 5 x $C\underline{H}_2$), 1.41-1.46 (2H, m, $NHCH_2C\underline{H}_2$), 2.82 (2H, aq, *J* 6.7 Hz, $C\underline{H}_2NHSO_2$), 6.37 (1H, t, *J* 5.5 Hz, $SO_2N\underline{H}$), 6.40 (2H, s, $N\underline{H}_2$); δ_C (100.5 MHz, DMSO) 14.4 (q, $\underline{C}H_3$), 22.5, 26.8, 29.1, 29.1, 29.4, 31.7 (6 x t, 6 x $\underline{C}H_2$), 43.0 (t, $\underline{C}H_2NH$); HRMS (ESI) calculated for $C_8H_{20}N_2NaO_2S$: 231.1143. Found: 231.1134 (MNa^+)

***N*-(Decyl)sulfamide 2.19c**



General Procedure B, using sulfamoylcarbamate **2.18c**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.3), afforded sulfamide **2.19c** (536 mg, 76 %) as a white solid; m.p. 83-86 °C (DCM); υ_{max} (neat) 3330 (N-H), 3270 (N-H), 1342 (s, S=O), 1135 (s, S=O); δ_H (400 MHz, DMSO) 0.84 (3H, t, *J* 6.4 Hz, C$\underline{H}_3$), 1.18-1.30 (14H, m, 7 x C$\underline{H}_2$), 1.39-1.44 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.82 (2H, aq, *J* 6.7 Hz, C$\underline{H}_2$NH), 6.36 (1H, t, *J* 5.5 Hz, N$\underline{H}$), 6.40 (2H, s, N$\underline{H}_2$); δ_C (100.5 MHz, DMSO) 14.4 (q, $\underline{C}H_3$), 22.6, 26.8, 29.2, 29.4, 29.5, 31.8 (6 x t, 8 x $\underline{C}H_2$), 43.0 (t, $\underline{C}H_2$NH); HRMS (ESI) calculated for $C_{10}H_{24}N_2NaO_2S$: 259.1456. Found: 259.1444 (MNa^+).

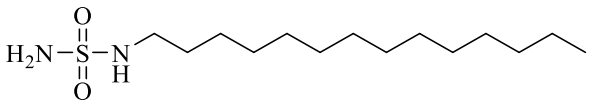
***N*-(Dodecyl)sulfamide 2.19d**



General Procedure B**,** using sulfamoylcarbamate **2.18d** and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.3), sulfamide **2.19d** (493 mg, 68 %) as a white solid; m.p. 95-96 °C (DCM); υ_{max} (neat) 3338 (N-H), 3278 (N-H), 1345 (s, S=O), 1136 (s, S=O); δ_H (400 MHz, DMSO) 0.84 (3H, t, *J* 6.4 Hz, C$\underline{H}_3$), 1.18-1.30 (18H, m, 9 x C$\underline{H}_2$), 1.39-1.44 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.82 (2H, aq, *J* 6.7 Hz, C$\underline{H}_2$NH),

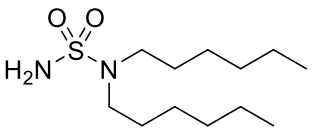
6.37 (1H, t, *J* 5.5 Hz, NH), 6.40 (2H, s, N<u>H</u>$_2$); δ_C (100.5 MHz, DMSO) 14.4 (q, <u>C</u>H$_3$), 22.5, 26.8, 29.2, 29.5, 29.5, 31.8 (6 x t, 10 x <u>C</u>H$_2$), 43.0 (t, <u>C</u>H$_2$NH); HRMS (ESI) calculated for $C_{12}H_{29}N_2O_2S$: 265.1950. Found: 265.1937 (MH^+).

_N_-(Tetradecyl)sulfamide 2.19e



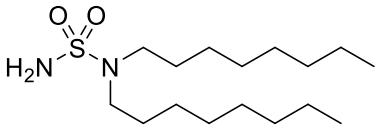
General Procedure B, using sulfamoylcarbamate **2.18e**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.4), afforded sulfamide **2.19e** (562 mg, 75 %) as a white solid; m.p. 99-101 °C (DCM); υ_{max} (neat) 3338 (N-H), 3276 (N-H), 1340 (s, S=O), 1134 (s, S=O); δ_H (400 MHz, DMSO) 0.84 (3H, t, *J* 6.4 Hz, C<u>H</u>$_3$), 1.18-1.32 (22H, m, 11 x C<u>H</u>$_2$), 1.37-1.44 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.82 (2H, aq, *J* 6.7 Hz, C<u>H</u>$_2$NH), 6.36 (1H, t, *J* 5.5 Hz, NH), 6.40 (2H, s, N<u>H</u>$_2$); δ_C (100.5 MHz, DMSO) 14.4 (q, <u>C</u>H$_3$), 22.5, 26.8, 29.2, 29.2, 29.5, 29.5, 31.7 (7 x t, 12 x <u>C</u>H$_2$), 43.0 (t, <u>C</u>H$_2$NH); HRMS (ESI) calculated for $C_{14}H_{33}N_2O_2S$: 293.2263. Found: 293.2252 (MH^+).

***N,N*-(Dihexyl)sulfamide 2.19f**



General Procedure B, using sulfamoylcarbamate **2.18f,** and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.5), afforded sulfamide **2.19f** (667 mg, 92 %) as a pale yellow solid; m.p. 55-58 °C (DCM); υ_{max} (neat) 3381 (N-H), 3264 (N-H), 1350 (s, S=O), 1137 (s, S=O); δ_H (400 MHz, $CDCl_3$) 0.89 (6H, t, *J* 6.4 Hz, 2 x C$\underline{H}_3$), 1.25-1.32 (12H, m, 6 x C$\underline{H}_2$), 1.54-1.63 (4H, m, 2 x NCH$_2$C$\underline{H}_2$), 3.15 (4H, t, *J* 7.8 Hz, 2 x C$\underline{H}_2$N); δ_C (100.5 MHz, $CDCl_3$) 14.0 (q, 2 x $\underline{C}H_3$), 22.6, 26.4, 28.1, 31.5 (4 x t, 8 x $\underline{C}H_2$), 48.4 (t, 2 x $\underline{C}H_2$N); HRMS (ESI) calculated for $C_{12}H_{29}N_2O_2S$: 265.1950. Found: 265.1937 (MH^+).

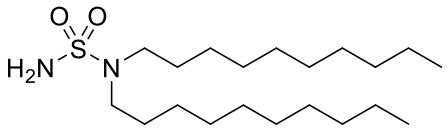
***N,N*-(Dioctyl)sulfamide 2.19g**



General Procedure B, using sulfamoylcarbamate **2.18g**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.5), afforded sulfamide **2.19g** (537 mg, 76 %) as a pale yellow solid; m.p. 48-50 °C (DCM); υ_{max} (neat) 3381 (N-H), 3264 (N-H), 1350 (s, S=O), 1137 (s, S=O); δ_H (400 MHz, $CDCl_3$) 0.88 (6H, t, *J* 6.4 Hz, 2 x C$\underline{H}_3$), 1.27-1.29 (20H, m, 10 x C$\underline{H}_2$), 1.55-1.63 (4H, m, 2 x NCH$_2$C$\underline{H}_2$), 3.15 (4H, t, *J* 7.8

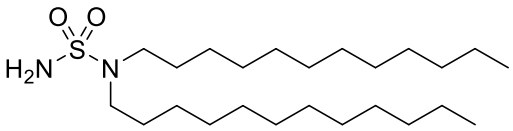
Hz, 2 x C$\underline{H}_2$N); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, 2 x $\underline{C}H_3$), 22.6, 26.8, 28.2, 29.2, 31.8 (5 x t, 12 x $\underline{C}H_2$), 48.4 (t, 2 x $\underline{C}H_2$N); HRMS (ESI) calculated for $C_{16}H_{37}N_2O_2S$: 321.2576. Found: 321.2565 (MH^+).

***N,N*-(Didecyl)sulfamide 2.19h**



General Procedure B, using sulfamoylcarbamate **2.18h**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.6), afforded sulfamide **2.19h** (521 mg, 66 %) as a pale yellow solid; m.p. 53-55 °C (DCM); υ_{max} (neat) 3392 (N-H), 3285 (N-H), 1350 (s, S=O), 1137 (s, S=O); δ_H (400 MHz, $CDCl_3$) 0.88 (6H, t, *J* 6.6 Hz, 2 x C$\underline{H}_3$), 1.26-1.29 (28H, m, 14 x C$\underline{H}_2$), 1.54-1.63 (4H, m, 2 x NCH$_2$C$\underline{H}_2$), 3.15 (4H, t, *J* 7.8 Hz, 2 x C$\underline{H}_2$N); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, 2 x $\underline{C}H_3$), 22.7, 26.8, 28.2, 29.3, 29.6, 31.9 (6 x t, 16 x $\underline{C}H_2$), 48.4 (t, 2 x $\underline{C}H_2$N); HRMS (ESI) calculated for $C_{20}H_{45}N_2O_2S$: 377.3202. Found: 377.3196 (MH^+).

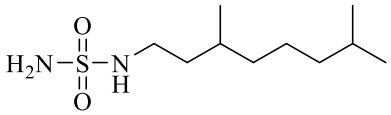
***N,N*-(Didodecyl)sulfamide 2.19i**



General Procedure B, using sulfamoylcarbamate **2.18i**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.6), afforded sulfamide **2.19i** (632 mg, 78

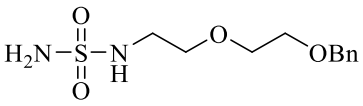
%) as a pale yellow solid; m.p. 58-60 °C (DCM); υ_{max} (neat) 3392 (N-H), 3285 (N-H), 1350 (s, S=O), 1137 (s, S=O); δ_H (400 MHz, $CDCl_3$) 0.88 (6H, t, *J* 6.6 Hz, 2 x CH_3), 1.25-1.29 (36H, m, 18 x CH_2), 1.54-1.62 (4H, m, 2 x $NCH_2C\underline{H}_2$), 3.15 (4H, t, *J* 7.2 Hz, 2 x $C\underline{H}_2N$); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, 2 x $\underline{C}H_3$), 22.7, 26.8, 28.2, 29.3, 29.6, 29.6, 31.9 (7 x t, 20 x $\underline{C}H_2$), 48.4 (t, 2 x $\underline{C}H_2N$); HRMS (ESI) calculated for $C_{24}H_{53}N_2O_2S$: 433.3828. Found: 433.3824 (MH^+).

***N*-(3,7-Dimethyloctyl)sulfamide 2.19j**



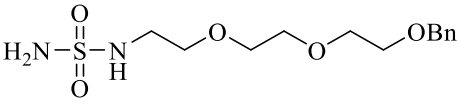
General Procedure B, using sulfamoylcarbamate **2.18j,** and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.4), afforded sulfamide **2.19j** (0.8 g, 98 %) as a yellowish brown waxy solid; υ_{max} (neat) 3275 (N-H), 1324 (w, S=O), 1137 (s, S=O); δ_H (500 MHz, $CDCl_3$) 0.85-0.91 (9H, m, 3 x CH_3), 1.11-1.15 (2H, m, $C\underline{H}_2$), 1.21-1.31 (2H, m, $C\underline{H}_2$), 1.35-1.41 (2H, m, $C\underline{H}_2$), 1.48-1.50 (2H, m, $C\underline{H}_2$), 1.51-1.64 (2H, m, 2 x $C\underline{H}$), 3.10-3.16 (2H, m, $C\underline{H}_2NHSO_2$), 4.40 (1H, s, $N\underline{H}$), 4.67 (2H, s, $N\underline{H}_2$); δ_C (125 MHz, $CDCl_3$) 19.3, 22.6, 22.7 (3 x q, 3 x $(\underline{C}H_3)_2$), 24.6 (t, $\underline{C}H_2$), 27.9, 30.4 (2 x d, 2 x $\underline{C}H$), 36.5, 37.1 (2 x t, 2 x $\underline{C}H_2$), 39.2 (t, $\underline{C}H_2$), 41.8 (t, $NH\underline{C}H_2$); HRMS (ESI) calculated for $C_{10}H_{25}N_2O_2S$: 237.1637 . Found: 237.1633 (MH^+).

***N*-(2-(2-(Benzyloxy)ethoxy)ethyl)sulfamide 2.19k**



General procedure B, using sulfamoylcarbamate **2.18k**, and purification by flash chromatography (DCM: MeOH, 19:1, R_f 0.2), afforded sulfamide **2.19k** (1.1 g, 88 %) as a yellowish brown waxy solid. υ_{max} (neat) 3253 (N-H), 1333 (s, S=O), 1127 (s, S=O); δ_H (400 MHz, $CDCl_3$) 3.34 (2H, t, *J* 4.0 Hz, C$\underline{H}_2$NH), 3.61-3.65 (6H, m, 3 x C$\underline{H}_2$), 4.54 (2H, s, PhC$\underline{H}_2$), 7.26-7.38 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 43.1 (t, $\underline{C}H_2$NH), 68.6, 69.7 (2 x t, 3 x CH_2), 72.8 (t, Ph-$\underline{C}H_2$), 127.8, 127.9, 128.4 (3 x d, 5 x Ar($\underline{C}$)H), 137.1 (s, Ar-$\underline{C}$); HRMS (ESI) calculated for $C_{11}H_{18}N_2NaO_4S$ 297.0855. Found 297.0870 (MNa^+).

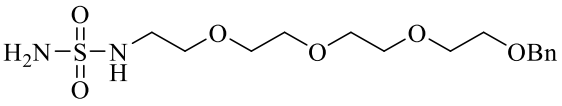
***N*-2-(2-(2-(Benzyloxy)ethoxy)ethoxy)ethyl)sulfamide 2.19l**



General procedure B, using sulfamoylcarbamate **2.18l**, and purification by flash chromatography (petrol: EtOAc, 1:2, R_f 0.3), afforded sulfamide **2.19l** (0.76 g, 76 %) as a yellow waxy solid. υ_{max} (neat) 3277 (N-H), 1335 (s, S=O), 1132 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.32 (2H, t, *J* 4.7 Hz, C$\underline{H}_2$NH), 3.62-3.68 (10H, m, 5 x C$\underline{H}_2$), 4.57 (2H, s, Ph-C$\underline{H}_2$), 7.26-7.36 (5H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 43.4 (t, $\underline{C}H_2$NH),

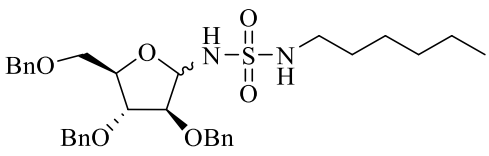
69.1, 69.7, 70.2, 70.3 (4 x t, 5 x $\underline{C}H_2$), 73.1 (t, Ph$\underline{C}H_2$), 127.8, 128.0, 128.4 (3 x d, 5 x Ar($\underline{C}$)H), 137.7 (s, Ar-$\underline{C}$); HRMS (ESI) calculated for $C_{13}H_{22}N_2NaO_5S$ 341.1147. Found 341.1142 (MNa^+).

_N_-2-(2-(2-(2-(Benzyloxy)ethoxy)ethoxy)ethoxy)ethyl)sulfamide 2.19m



General procedure B, using sulfamoylcarbamate **2.18m**, and purification by flash chromatography (petrol: ethyl acetate, 1:2, R_f 0.2), afforded sulfamide **2.19m** (0.15 g, 65 %) as a yellow waxy solid. υ_{max} (neat) 3251 (N-H), 1332 (s, S=O), 1082 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.29 (2H, t, *J* 4.0 Hz, $C\underline{H}_2NH$), 3.59-3.65 (14H, m, 7 x $C\underline{H}_2$), 4.58 (2H, s, Ph$C\underline{H}_2$), 7.26-7.35 (5H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 43.6 (t, $\underline{C}H_2NH$), 69.2, 69.6, 69.9, 70.2 (4 x t, 7 x $\underline{C}H_2$), 73.2 (t, Ph$\underline{C}H_2$), 127.7, 128.1, 128.4 (3 x d, 3 x Ar($\underline{C}$)H), 137.9 (s, Ar-$\underline{C}$); HRMS (ESI) calculated for $C_{15}H_{26}N_2NaO_6S$ 385.1409. Found 385.1400 (MNa^+).

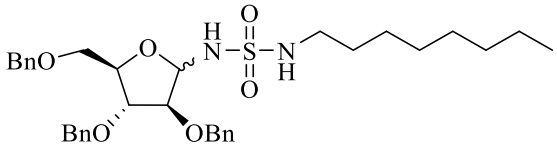
_N_-(Hexyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20a



General Procedure C, using sulfamide **2.19a**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.4), afforded glycosylsulfamide **2.20a** (280

mg, 52 %, α:β, 1:1) as a yellow waxy solid; υ_{max} (neat) 3285 (NH), 1350 (s, S=O), 1158 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.89 (3H, t, *J* 6.8 Hz, C<u>H</u>$_3$), 1.24-1.36 (6H, m, 3 x C<u>H</u>$_2$), 1.48-1.55 (2H, m, NHCH$_2$C<u>H</u>$_2$), 3.00-3.04 (2H, m, C<u>H</u>$_2$NH), 3.48 (1H, d, *J* 7.0 Hz, H-5), 3.55 (1H, d, *J* 5.8 Hz, H-5'), 3.94-4.03 (2H, m, H-2, H-3), 4.34 (1H, d, *J* 7.0 Hz, H-4), 4.47-4.59 (6H, m, Ph-C<u>H</u>$_2$), 5.44 (1H, d, $J_{NH,1}$ 11.8 Hz, H-1), 5.52-5.64 (1H, m, N<u>H</u>), 7.16-7.42 (15H, m, Ar-H); β anomer: 0.89 (3H, m, C<u>H</u>$_3$), 1.24-1.36 (6H, m, 3 x C<u>H</u>$_2$), 1.48-1.55 (2H, m, NHCH$_2$C<u>H</u>$_2$), 3.00-3.03 (2H, m, C<u>H</u>$_2$NH), 3.53 (2H, dd, $J_{5,5'}$ 7.0 Hz, $J_{4,5}$ 5.5 Hz, H-5, H-5'), 3.94-4.04 (3H, m, H-2, H-3, H-4), 4.47-4.59 (6H, m, Ph-C<u>H</u>$_2$), 5.37 (1H, dd, $J_{1,NH}$ 6.8 Hz, $J_{1,2}$ 4.5 Hz, H-1), 5.52-5.64 (1H, m, N<u>H</u>), 7.16-7.42 (15H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 14.0 (q, CH_3), 22.5, 26.3, 29.4, 31.4 (4 x t, 4 x CH_2), 43.4, 43.5 (2 x t, NHCH$_2$α, NHCH$_2$β), 70.0, 70.1(2 x t, C-5α, C-5β), 71.8, 71.8, 72.0, 72.3, 73.4, 73.4 (6 x t, Ph<u>C</u>H$_2$), 80.8 (d, C-4β), 81.2, 81.8 (2 x d, C-2α, C-2β), 82.4 (C-3β), 83.3 (d, C-4α), 84.3 (d, C-1β), 84.8 (d, C-3α), 88.2 (d, C-1α), 127.7, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.0, 128.2, 128.2, 128.3, 128.4, 128.5, 128.5, 128.6 (15 x d, 15 x Ar(<u>C</u>)H), 136.7, 136.8, 136.9, 137.4, 137.6, 137.9 (6 x s, 6 x Ar-<u>C</u>); HRMS (ESI) calculated for $C_{32}H_{42}N_2NaO_6S$: 605.2661. Found: 605.2656 (MNa^+).

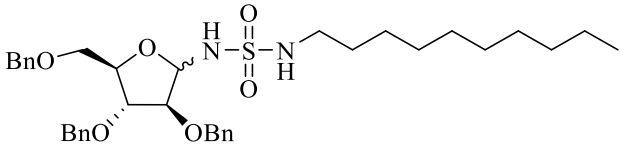
_N_-(Octyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20b



General Procedure C, using sulfamide **2.19b**, and purification by flash chromatography (petrol: EtOAc , 2:1, R_f 0.4), afforded glycosylsulfamide sulfamide

2.20b (230 mg, 54 %, α:β, 1:1) as a yellow waxy solid; υ_{max} (neat) 3280 (N-H), 1350 (s, S=O), 1158 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.88 (3H, t, *J* 6.6 Hz, C<u>H</u>$_3$), 1.19-1.36 (10H, m, 5 x C<u>H</u>$_2$), 1.48-1.55 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.98-3.03 (2H, m, C<u>H</u>$_2$NH), 3.48 (1H, dd, $J_{5,5'}$ 9.6 Hz, $J_{4,5'}$ 7.6 Hz, H-5), 3.58 (1H, dd, $J_{5,5'}$ 9.8 Hz, $J_{4,5'}$ 5.9 Hz, H-5'), 3.94-3.97 (1H, m, H-3), 3.98 (1H, at, *J* 3.1 Hz, H-2), 4.34 (1H, at, *J* 6.7 Hz, H-4), 4.40-4.61 (6H, m, Ph-C<u>H</u>$_2$), 5.41 (1H, d, $J_{NH,1}$ 10.6 Hz, H-1), 5.52-5.61 (1H, m, N<u>H</u>), 7.19-7.44 (15H, m, Ar-H); β anomer: 0.88 (3H, m, C<u>H</u>$_3$), 1.19-1.36 (10H, m, 5 x C<u>H</u>$_2$), 1.48-1.55 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.98-3.03 (2H, m, C<u>H</u>$_2$NH), 3.52 (2H, d, *J* 5.1 Hz, H-5, H-5'), 3.94-3.97 (1H, m, H-3), 4.01 (1H, at, $J_{1,2}$ 4.3 Hz, H-2), 4.05 (1H, dd, $J_{4,5}$ 5.1 Hz,$J_{3,4}$ 3.5 Hz, H-4), 4.40-4.61 (6H, m, Ph-C<u>H</u>$_2$), 5.37 (1H, dd, $J_{NH,1}$ 10.2 Hz, $J_{1,2}$ 4.3Hz, H-1), 5.52-5.61 (1H, m, N<u>H</u>), 7.19-7.44 (15H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, CH_3), 22.6, 26.7, 29.2, 29.4, 31.8 (5 x t, 6 x CH_2), 43.4, 43.5 (2 x t, NHCH$_2$α, NHCH$_2$β), 70.0, 70.1 (2 x t, C-5α, C-5β), 71.7, 71.8, 72.0, 72.3, 73.3, 73.4 (6 x t, Ph<u>C</u>H$_2$), 80.8 (d, C-4β), 81.2, 81.8 (2 x d, C-2α, C-2β), 82.4 (C-3β), 83.3 (d, C-4α), 84.2 (d, C-1β), 84.8 (d, C-3α), 88.2 (d, C-1α), 127.7, 127.7, 127.8, 127.9,127.9, 127.9, 127.9, 128.1, 128.2, 128.2, 128.3, 128.4, 128.5, 128.5, 128.6 (15 x d, 15 x Ar-<u>C</u>), 136.7, 136.7, 136.8, 137.4, 137.7, 137.9 (6 x s, 6 x Ar-<u>C</u>); HRMS (ESI) calculated for $C_{34}H_{46}N_2NaO_6S$: 633.2974. Found: 633.2976 (MNa^+).

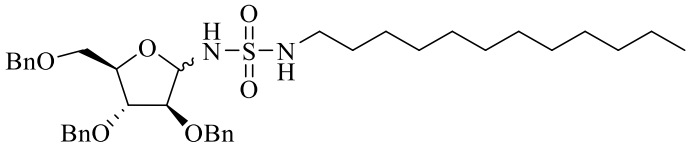
_N_-(Decyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20c



General Procedure C, using sulfamide **2.19c**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.4), afforded glycosylsulfamide **2.20c** (470

mg, 77 %, α:β, 1:1) as a yellow waxy solid; υ_{max} (neat)) 3280 (N-H), 1350 (s, S=O), 1158 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.89 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$), 1.24-1.29 (14H, m, 7 x C$\underline{H}_2$), 1.48-1.53 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.98-3.03 (2H, m, C$\underline{H}_2$NH), 3.46-3.50 (1H, m, H-5), 3.58 (1H, dd, $J_{5,5'}$ 8.6 Hz, $J_{4,5'}$ 6.7 Hz, H-5'), 3.95-3.97 (1H, m, H-3), 3.98-4.02 (1H, m, H-2), 4.34 (1H, at, *J* 6.6 Hz, H-4), 4.38-4.63 (6H, m, Ph-C$\underline{H}_2$), 5.42 (1H, d, $J_{NH,1}$ 10.5 Hz, H-1), 5.54 (1H, d, $J_{NH,1}$ 11.0 Hz N$\underline{H}$), 7.15-7.40 (15H, m, Ar-H); β anomer: 0.89 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$), 1.24-1.29 (14H, m, 7 x C$\underline{H}_2$), 1.48-1.53 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.98-3.03 (2H, m, C$\underline{H}_2$NH), 3.52-3.54 (1H, m, H-5, H-5'), 3.95-3.97 (1H, m, H-3), 3.98-4.02 (1H, m, H-2), 4.05-4.06 (1H, m, H-4), 4.38-4.63 (6H, m, Ph-C$\underline{H}_2$), 5.37 (1H, dd, $J_{NH,1}$ 10.2 Hz, $J_{1,2}$ 4.3 Hz, H-1), 5.52 (1H, d, $J_{NH,1}$ 10.8 Hz N$\underline{H}$), 7.15-7.40 (15H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, CH_3), 22.7, 26.7, 29.2, 29.3, 29.4, 29.5, 29.5, 31.8, (8 x t, 8 x CH_2), 43.4, 43.5 (2 x t, NHCH$_2$α, NHCH$_2$β), 70.1 (t, C-5α, C-5β), 71.8, 71.8, 72.0, 72.3, 73.3, 73.4 (6 x t, Ph-C$\underline{H}_2$), 80.8 (d, C-4β), 81.2, 81.8 (2 x d, C-2α, C-2β), 82.4 (d, C-3β), 83.3 (d, C-4α), 84.3 (d, C-1β), 84.8 (d, C-3α), 88.2 (d, C-1α), 127.7, 127.7, 127.7, 127.8, 127.9, 127.9, 128.1, 128.2, 128.2, 128.3, 128.4, 128.5, 128.5, 128.5, 128.6 (15 x d, 15 x Ar-C), 136.7, 136.8, 136.9, 137.4, 137.7, 137.9 (6 x s, 6 x Ar-C); HRMS (ESI) calculated for $C_{36}H_{50}N_2NaO_6S$: 661.3287. Found 661.3288 (MNa^+).

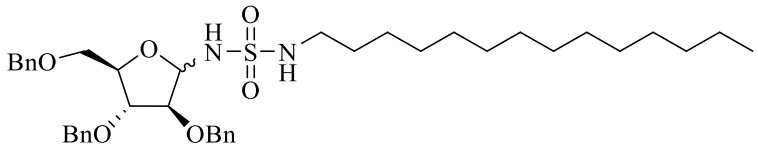
_N_-(Dodecyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20d



General Procedure C, using sulfamide **2.19d**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.4), afforded glycosylsulfamide **2.20d** (450

mg, 71 %, α:β, 1:1) as a yellow waxy solid; υ_{max} (neat) 3286 (N-H), 1344 (s, S=O), 1151 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.89 (3H, t, *J* 6.9 Hz, C<u>H</u>$_3$), 1.20-1.38 (18H, m, 9 x C<u>H</u>$_2$), 1.44-1.65 (2H, m, C<u>H</u>$_2$), 3.00 (2H, t, *J* 6.7 Hz, C<u>H</u>$_2$NH), 3.47 (1H, dd, $J_{5,5'}$ 9.8 Hz, $J_{4,5'}$ 7.4 Hz, H-5), 3.58 (1H, dd, $J_{5,5'}$ 9.6 Hz, $J_{4,5'}$ 6.1 Hz, H-5'), 3.94-3.97 (1H, m, H-3), 3.98 (1H, at, *J* 3.1 Hz, H-2), 4.34 (1H, at, *J* 5.9 Hz, H-4), 4.40-4.67 (6H, m, Ph-C<u>H</u>$_2$), 5.42 (1H, d, $J_{NH,1}$ 10.5 Hz, H-1), 5.57 (1H, at, *J* 11.3 Hz, N<u>H</u>), 7.18-7.41 (15H, m, Ar-H); β anomer: 0.89 (3H, t, *J* 6.9 Hz, C<u>H</u>$_3$), 1.20-1.38 (18H, m, 9 x C<u>H</u>$_2$), 1.44-1.65 (2H, m, C<u>H</u>$_2$), 3.00 (2H, t, *J* 6.7 Hz, C<u>H</u>$_2$NH), 3.52 (2H, d, *J* 5.1 Hz, H-5, H-5'), 3.94-3.97 (1H, m, H-3), 4.01 (1H, at, $J_{1,2}$ 4.3 Hz, H-2), 4.05 (1H, dd, $J_{4,5}$ 5.1 Hz,$J_{3,4}$ 3.5 Hz, H-4), 4.40-4.67 (6H, m, Ph-C<u>H</u>$_2$), 5.37 (1H, dd, $J_{NH,1}$ 10.2 Hz, $J_{1,2}$ 4.3Hz, H-1), 5.57 (1H, t, *J* 11.3 Hz, N<u>H</u>), 7.18-7.41 (15H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, CH_3), 22.7, 26.7, 26.7, 29.2, 29.3, 29.4, 29.6, 29.6, 29.7, 31.9 (10 x t, 10 x CH_2), 43.4, 43.5 (2 x t, $NHCH_2\alpha$, $NHCH_2\beta$), 70.0, 70.1(2 x t, C-5α, C-5β), 71.7, 71.8, 72.0, 72.3, 73.3, 73.4 (6 x t, Ph-<u>C</u>H$_2$), 80.8 (d, C-4β), 81.2, 81.8 (2 x d, C-2α, C-2β), 82.4 (d, C-3β), 83.3 (d, C-4α), 84.3 (d, C-1β), 84.8 (d, C-3α), 88.2 (d, C-1α), 127.7, 127.7, 127.8, 127.9, 127.9, 127.9, 128.0, 128.1, 128.2, 128.2, 128.4, 128.5, 128.5, 128.5, 128.6 (15 x d, 15 x Ar-<u>C</u>), 136.7, 136.7, 136.9, 137.4, 137.7, 137.9 (6 x s, 6 x Ar-<u>C</u>); HRMS (ESI) calculated for $C_{38}H_{54}N_2NaO_6S$: 689.3600. Found: 689.3600 (MNa^+).

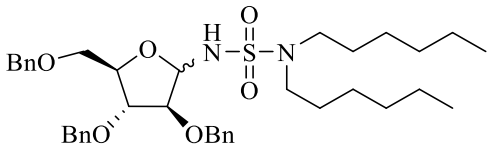
_N_-(Tetradecyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20e



General Procedure C, sulfamide **2.19e**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.4), afforded glycosylsulfamide **2.20e** (360 mg, 54 %, α:β, 1:1) as a yellow waxy solid; υ_{max} (neat) 3280 (N-H), 1350 (s, S=O), 1158 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.90 (3H, t, *J* 6.6 Hz, C<u>H</u>$_3$), 1.21-1.38 (22H, m, 11 x C<u>H</u>$_2$), 1.44-1.74 (2H, m, C<u>H</u>$_2$), 3.01 (2H, t, *J* 7.2 Hz, C<u>H</u>$_2$NH), 3.49 (1H, dd, $J_{5,5'}$ 9.8 Hz, $J_{4,5'}$ 7.4 Hz, H-5), 3.59 (1H, dd, $J_{5,5'}$ 9.8 Hz, $J_{4,5'}$ 5.9 Hz, H-5'), 3.94-3.97 (1H, m, H-3), 4.00 (1H, at, *J* 3.1 Hz, H-2), 4.35 (1H, at, *J* 6.6 Hz, H-4), 4.43-4.65 (6H, m, Ph-C<u>H</u>$_2$), 5.43 (1H, d, $J_{NH,1}$ 10.6 Hz, H-1), 5.62 (1H, d, $J_{NH,1}$ 10.9, N<u>H</u>), 7.20-7.46 (15H, m, Ar-H); β anomer: 0.90 (3H, t, *J* 6.6 Hz, C<u>H</u>$_3$), 1.21-1.38 (22H, m, 11 x C<u>H</u>$_2$), 1.44-1.74 (2H, m, C<u>H</u>$_2$), 2.98-3.01 (2H, t, *J* 7.2 Hz, C<u>H</u>$_2$NH), 3.54 (2H, d, *J* 5.1 Hz, H-5, H-5'), 3.94-3.97 (1H, m, H-3), 4.03 (1H, at, $J_{1,2}$ 4.3 Hz, H-2), 4.06 (1H, dd, $J_{4,5}$ 5.1 Hz,$J_{3,4}$ 3.5 Hz, H-4), 4.43-4.65 (6H, m, Ph-C<u>H</u>$_2$), 5.38 (1H, dd, $J_{NH,1}$ 10.4 Hz, $J_{1,2}$ 4.5Hz, H-1), 5.58 (1H, d, $J_{NH,1}$10.4 Hz N<u>H</u>), 7.20-7.46 (15H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, CH_3), 22.7, 26.7, 26.7, 29.2, 29.4, 29.5, 29.5, 29.6, 29.7, 29.7, 29.7, 31.9 (12 x t, 12 x CH_2), 43.4, 43.5 (2 x t, $NHCH_2\alpha$, $NHCH_2\beta$), 70.1 (t, C-5α, C-5β), 71.8, 72.0, 72.2, 72.3, 73.4, 73.5 (6 x t, Ph-<u>C</u>H$_2$), 80.8 (d, C-4β), 81.2, 81.8 (2 x d, C-2α, C-2β), 82.4 (d, C-3β), 83.2 (d, C-4α), 84.3 (d, C-1β), 84.9 (d, C-3α), 88.2 (d, C-1α), 127.7, 127.7, 127.8, 127.8, 127.9, 128.0, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5,128.5, 128.6 (15 x d, 15 x Ar-<u>C</u>), 136.7, 136.8, 136.9, 137.9, 137.9,

138.1 (6 x s, 6 x Ar-C); HRMS (ESI) calculated for $C_{40}H_{58}N_2NaO_6S$: 717.3913. Found: 717.3910 (MNa^+).

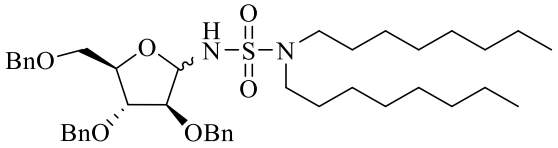
_N_-(Dihexyl)-_N'_-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20f



General Procedure C, using sulfamide **2.19f**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.6), afforded glycosylsulfamide **2.20f** (250 mg, 78 %, α:β, 1:1) as a yellow waxy solid; υ_{max} (neat) 3288 (N-H), 1350 (s, S=O), 1158 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.89 (6H, t, *J* 6.7 Hz, 2 x C<u>H</u>$_3$), 1.17-1.37 (12H, m, 6 x C<u>H</u>$_2$), 1.51-1.63 (4H, m, 2 x NCH$_2$C<u>H</u>$_2$), 2.97-3.25 (4H, m, 2 x C<u>H</u>$_2$NH), 3.50 (1H, dd, $J_{5,5'}$ 9.8 Hz, $J_{4,5'}$ 7.8 Hz, H-5), 3.60 (1H, dd, $J_{5,5'}$ 9.8 Hz, $J_{4,5'}$ 5.9 Hz, H-5'), 3.95-3.97 (1H, m, H-3), 3.99-4.02 (1H, m, H-2), 4.35 (1H, at, *J* 6.7 Hz, H-4), 4.42-4.64 (6H, m, Ph-C<u>H</u>$_2$), 5.36 (1H, d, $J_{NH,1}$ 10.5 Hz, H-1), 5.47 (1H, d, $J_{NH,1}$ 8.0 Hz, N<u>H</u>), 7.18-7.44 (15H, m, Ar-H); β anomer: 0.89 (6H, t, *J* 6.7 Hz, 2 x C<u>H</u>$_3$), 1.17-1.37 (12H, m, 6 x C<u>H</u>$_2$), 1.51-1.63 (4H, m, 2 x NHCH$_2$C<u>H</u>$_2$), 2.97-3.25 (4H, m, 2 x C<u>H</u>$_2$NH), 3.54 (2H, at, *J* 5.1 Hz, H-5, H-5'), 3.95-3.97 (1H, m, H-3), 3.99-4.02 (1H, m, H-2), 4.03-4.07 (1H, m, H-4), 4.42-4.64 (6H, m, Ph-C<u>H</u>$_2$), 5.31 (1H, dd, $J_{NH,1}$ 9.8Hz, $J_{1,2}$ 3.1 Hz, H-1), 5.43 (1H, d, $J_{NH,1}$ 8.5 Hz, N<u>H</u>), 7.18-7.44 (15H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 14.0 (q, 2 x CH_3), 22.6, 26.5, 28.7, 31.5, (4 x t, 8 x CH_2), 48.8 (t, 2 x <u>C</u>H$_2$N), 70.2, 70.2 (t, C-5α, C-5β), 71.7, 71.8, 71.8, 72.3, 73.3, 73.4 (6 x t, Ph-<u>C</u>H$_2$), 80.5 (d, C-4β), 81.5, 81.9 (2 x d, C-2α, C-2β), 82.5 (d, C-3β), 82.8 (d, C-4α), 84.0 (d, C-1β), 85.1 (d, C-3α), 87.8 (d, C-1α), 127.7, 127.7, 127.7, 127.8, 127.9,

128.0, 128.1, 128.1, 128.2, 128.4, 128.4, 128.5, 128.5, 128.6 (14 x d, 14 x Ar-C), 136.9, 136.9, 137.1, 137.6, 137.8, 138.0 (6 x s, 6 x Ar-C); HRMS (ESI) calculated for $C_{38}H_{55}N_2O_6S$: 667.3781. Found: 667.3790 (MH^+).

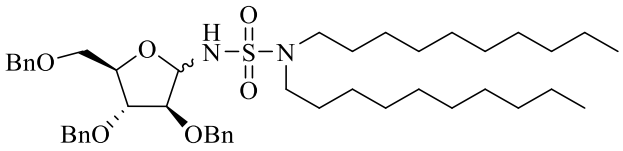
_N_-(Dioctyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20g



General Procedure C, using sulfamide **2.19g**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.6), afforded glycosylsulfamide **2.20g** (230 mg, 68 %, α:β, 1:1) as a yellow waxy solid; υ_{max} (neat) 3282 (N-H), 1350 (s, S=O), 1158 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.88 (6H, t, *J* 6.7 Hz, 2 x C<u>H</u>$_3$), 1.21-1.33 (20H, m, 10 x C<u>H</u>$_2$), 1.51-1.60 (4H, m, 2 x NHCH$_2$C<u>H</u>$_2$), 2.99-3.25 (4H, m, 2 x C<u>H</u>$_2$NH),), 3.48 (1H, dd, $J_{5,5'}$ 9.8 Hz, $J_{4,5'}$ 8.2 Hz, H-5), 3.59 (1H, dd, $J_{5,5'}$ 9.6 Hz, $J_{4,5'}$ 5.7 Hz, H-5'), 3.93-3.96 (1H, m, H-3), 3.97-4.00 (1H, m, H-2), 4.32 (1H, at, *J* 6.5 Hz, H-4), 4.41-4.62 (6H, m, Ph-C<u>H</u>$_2$), 5.33 (1H, d, J_{NH-1} 11.9 Hz, H-1), 5.42 (1H, d, *J* 9.8 Hz, NH), 7.20-7.38 (15H, m, Ar-H); β anomer: 0.88 (6H, m, 2 x CH_3), 1.26 (20H, m, 10 x CH_2), 1.55 (4H, m, 2 x NCH$_2$C<u>H</u>$_2$), 2.99-3.25 (4H, m, 2 x C<u>H</u>$_2$NH), 3.53 (2H, at, *J* 4.3 Hz, H-5, H-5'), 3.93-3.96 (1H, m, H-3), 3.97-4.00 (1H, m, H-2), 4.01-4.04 (1H, m, H-4), 4.41-4.62 (6H, m, Ph-CH_2), 5.29 (1H, dd, $J_{NH,1}$ 10.2 Hz, $J_{1,2}$ 3.9 Hz, H-1), 5.42 (1H, d, *J* 9.8 Hz, NH), 7.20-7.38 (15H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, 2 x CH_3), 22.6, 26.8, 28.7, 28.8, 29.2, 29.3, 31.8 (7 x t, 12 x CH_2), 48.8, 48.9 (2 x t, 2 x <u>C</u>H$_2$N), 70.1, 70.2 (t, C-5α, C-5β), 71.7, 71.8, 71.8, 72.3, 73.3, 73.4 (6 x t, Ph-<u>C</u>H$_2$), 80.5 (d, C-4β), 81.5, 81.9 (2 x d, C-2α, C-2β), 82.5 (d, C-3β), 82.8 (d, C-

4α), 84.0 (d, C-1β), 85.1 (d, C-3α), 87.9 (d, C-1α), 127.6, 127.7, 127.7, 127.8, 127.9, 128.0, 128.1, 128.1, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6 (14 x d, 14 x Ar-C), 136.8, 136.9, 137.0, 137.5, 137.8, 138.0 (6 x s, 6 x Ar-C); HRMS (ESI) calculated for $C_{42}H_{63}N_2O_6S$: 723.4407. Found: 723.4416 (MH^+).

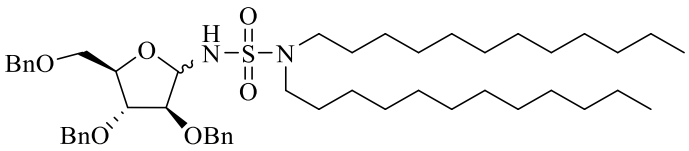
_N_-(Didecyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20h



General Procedure C, using sulfamide **2.19h**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.6), afforded glycosylsulfamide **2.20h** (320 mg, 59 %, α:β, 1:1) as a yellow waxy solid. υ_{max} (neat) 3285 (N-H), 1350 (s, S=O), 1158 (s, S=O) cm^{-1}; 0.88 (6H, t, *J* 6.7 Hz, 2 x C$\underline{H}_3$), 1.18-1.35 (28H, m, 14 x C$\underline{H}_2$), 1.50-1.61 (4H, m, 2 x NHCH$_2$C$\underline{H}_2$), 3.00-3.19 (4H, m, 2 x C$\underline{H}_2$NH), 3.49 (1H, dd, $J_{5,5'}$ 9.7 Hz, $J_{4,5'}$ 7.4 Hz, H-5), 3.58 (1H, dd, $J_{5,5'}$ 10.0 Hz, $J_{4,5'}$ 5.7 Hz, H-5'), 3.94-3.97 (1H, m, H-3), 3.97-4.00 (1H, m, H-2), 4.33 (1H, at, *J* 6.8 Hz, H-4), 4.42-4.58 (6H, m, Ph-C$\underline{H}_2$), 5.34 (1H, d, $J_{NH,1}$ 10.5 Hz, H-1), 5.43 (1H, d, *J* 9.7 Hz, NH), 7.22-7.38 (15H, m, Ar-H); β anomer: 0.88 (6H, t, *J* 6.7 Hz, 2 x C$\underline{H}_3$), 1.18-1.35 (28H, m, 14 x C$\underline{H}_2$), 1.50-1.61 (4H, m, 2 x NHCH$_2$C$\underline{H}_2$), 3.04-3.21 (4H, m, 2 x C$\underline{H}_2$NH), 3.54 (2H, at, *J* 4.7 Hz, H-5, H-5'), 3.94-3.97 (1H, m, H-3), 3.97-4.00 (1H, m, H-2), 4.02-4.04 (1H, m, H-4), 4.39-4.61 (6H, m, Ph-CH$_2$), 5.29 (1H, dd, $J_{NH,1}$ 9.8 Hz, $J_{1,2}$ 3.9 Hz, H-1), 5.43 (1H, d, *J* 9.7 Hz, NH), 7.22-7.38 (15H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, 2 x CH_3), 22.6, 26.8, 26.8, 28.8, 28.8, 29.3, 29.4, 29.6, 29.6, 31.9 (10 x t, 20 x CH_2), 48.9, 48.9 (2 x t, 2 x $\underline{C}H_2N$), 70.2, 70.2 (2 x t, C-5α, C-5β), 71.7, 71.8, 71.8,

72.3, 73.3, 73.4 (6 x t, Ph-$\underline{C}H_2$), 80.5 (d, C-4β), 81.5, 81.9 (2 x d, C-2α, C-2β), 82.5 (d, C-3β), 82.7 (d, C-4α), 84.0 (d, C-1β), 85.1 (d, C-3α), 87.8 (d, C-1α), 127.7, 127.7, 127.7, 127.8, 127.9, 127.9, 128.1, 128.1, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6 (15 x d, 15 x Ar-$\underline{C}$), 136.9, 136.9, 137.1, 137.6, 137.8, 138.0 (6 x s, 6 x Ar-$\underline{C}$); HRMS (ESI) calculated for $C_{46}H_{71}N_2O_6S$ 779.5033. Found 779.5045 (MH^+).

***N*-(Didodecyl)-*N'*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20i**

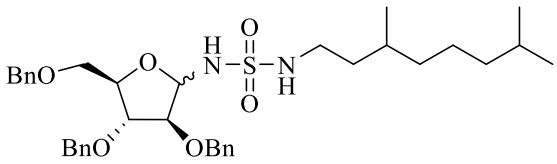


General Procedure C, using sulfamide **2.19i**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.6), afforded glycosylsulfamide **2.20i** (280 mg, 47 %, α:β, 1:1) as a yellow waxy solid. υ_{max} (neat) 3265 (N-H), 1350 (s, S=O), 1158 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.89 (6H, t, *J* 6.5 Hz, 2 x C$\underline{H}_3$), 1.12-1.37 (36H, m, 18 x C$\underline{H}_2$), 1.52-1.61 (4H, m, 2 x NHCH$_2$C$\underline{H}_2$), 3.04-3.21 (4H, m, 2 x C$\underline{H}_2$NH), 3.49 (1H, dd, $J_{5,5'}$ 9.7 Hz, $J_{4,5'}$ 7.4 Hz, H-5), 3.59 (1H, dd, $J_{5,5'}$ 10.0 Hz, $J_{4,5'}$ 5.7 Hz, H-5'), 3.94-3.97 (1H, m, H-3), 3.97-4.00 (1H, m, H-2), 4.33 (1H, at, *J* 6.8 Hz, H-4), 4.42-4.58 (6H, m, Ph-C$\underline{H}_2$), 5.35 (1H, d, $J_{NH,1}$ 10.5 Hz, H-1), 5.43 (1H, d, *J* 9.7 Hz, NH), 7.22-7.38 (15H, m, Ar-H); β anomer: 0.89 (6H, t, *J* 6.5 Hz, 2 x C$\underline{H}_3$), 1.12-1.37 (36H, m, 18 x C$\underline{H}_2$), 1.52-1.61 (4H, m, 2 x NHCH$_2$C$\underline{H}_2$), 3.04-3.21 (4H, m, 2 x C$\underline{H}_2$NH), 3.54 (2H, at, *J* 4.7 Hz, H-5, H-5'), 3.94-3.97 (1H, m, H-3), 3.97-4.00 (1H, m, H-2), 4.02-4.04 (1H, m, H-4), 4.39-4.61 (6H, m, Ph-CH_2), 5.30 (1H, dd, $J_{NH,1}$ 9.8 Hz, $J_{1,2}$ 3.9 Hz, H-1), 5.43 (1H, d, *J* 9.7 Hz, NH), 7.22-7.38 (15H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, 2 x CH_3), 22.7, 26.8, 28.8, 28.8, 29.4, 29.6, 29.6, 29.7,

29.7, 31.7 (10 x t, 20 x CH_2), 48.9, 48.9 (2 x t, 2 x $\underline{C}H_2N$), 70.2, 70.2 (2 x t, C-5α, C-5β), 71.7, 71.8, 71.8, 72.3, 73.3, 73.4 (6 x t, Ph-$\underline{C}H_2$), 80.5 (d, C-4β), 81.5, 81.9 (2 x d, C-2α, C-2β), 82.5 (d, C-3β), 82.8 (d, C-4α), 84.0 (d, C-1β), 85.1 (d, C-3α), 87.9 (d, C-1α), 127.6, 127.7,127.7, 127.8, 127.8, 127.9, 127.9, 128.1, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6 (15 x d, 15 x Ar-$\underline{C}$), 136.8, 136.9, 137.0, 137.8, 137.9, 138.0 (6 x s, 6 x Ar-$\underline{C}$); HRMS (ESI) calculated for $C_{50}H_{79}N_2O_6S$ 835.5659. Found 835.5667 (MH^+).

_N_-(3,7-Dimethyloctyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide

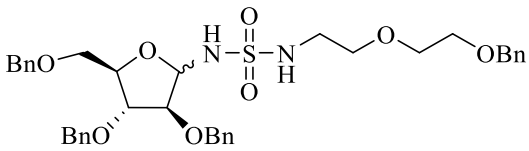
2.20j



General Procedure C, using sulfamide **2.19j**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.6), afforded glycosyl sulfamide **2.20j** (250 mg, 80 %, α:β, 1:1) as a yellow waxy solid. υ_{max} (neat) 3270 (w, NH), 1337 (s, S=O), 1071 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.88 (9H, d, *J* 6.7 Hz, 3 x CH_3), 1.10-1.16 (2H, m, $C\underline{H}_2$), 1.20-1.32 (4H, m, 2 x $C\underline{H}_2$), 1.48-1.58 (4H, m, 2 x CH, $C\underline{H}_2$), 3.02-3.07 (2H, m, $C\underline{H}_2NHSO_2$), 3.48 (1H, dd, $J_{5,5'}$ 9.6 Hz, $J_{4,5'}$ 7.6 Hz, H-5), 3.58 (1H, dd, $J_{5,5'}$ 9.6 Hz, $J_{4,5'}$ 5.7 Hz, H-5'), 3.94-3.97 (1H, m, H-3), 3.98-4.00 (1H, at, *J* 3.1 Hz, H-2), 4.35 (1H, at, *J* 6.8 Hz, H-4), 4.45-4.57 (6H, m, Ph-$C\underline{H}_2$), 5.42 (1H, d, $J_{1,NH}$ 10.6 Hz, H-1), 5.61 (1H, d, J_{NH-1} 10.6 Hz, NH), 7.22-7.37 (15H, m, Ar-H); β anomer: 0.88 (9H, d, *J* 6.7 Hz, 3 x CH_3), 1.10-1.16 (2H, m, $C\underline{H}_2$), 1.20-1.32 (4H, m, 2 x $C\underline{H}_2$), 1.48-1.58 (4H, m, 2 x CH, $C\underline{H}_2$), 3.02-3.07 (2H, m, $C\underline{H}_2NHSO_2$), 3.54 (2H, at, *J* 5.1

Hz, H-5, H-5'), 3.94-3.97 (1H, m, H-3), 4.01-4.02 (1H, at, *J* 4.7 Hz, H-2), 4.04-4.07 (1H, dd, $J_{4,5}$ 5.1 Hz, $J_{3,4}$ 3.5 Hz, H-4), 4.45-4.57 (6H, m, Ph-C$\underline{H}_2$), 5.37 (1H, dd, $J_{1,NH}$ 10.2 Hz, $J_{1,2}$ 4.3 Hz, H-1), 5.57 (1H, d, $J_{1,NH}$ 10.2 Hz, NH), 7.22-7.37 (15H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 19.3, 22.6, 22.7 (3 x q, 3 x $\underline{C}H_3$), 24.6 (t, $\underline{C}H_2$), 27.9, 30.4 (2 x d, 2 x $\underline{C}$H), 36.6, 36.6 (2 x t, 2 x $\underline{C}H_2$), 39.2 (t, $\underline{C}H_2$), 41.5, 41.6 (2 x t, NH$\underline{C}H_2$α, NH$\underline{C}H_2$ β), 70.0 (t, C-5α, C-5β), 71.8, 71.8, 72.0, 72.3, 73.3, 73.4 (6 x t, Ph$\underline{C}H_2$), 80.8 (d, C-4β), 81.2, 81.8 (2 x d, C-2α, C-2β), 82.3 (d, C-3β), 83.3 (d, C-4α,), 84.3 (d, C-1β), 84.8 (d, C-3α,), 88.2 (d, C-1α), 127.7, 127.7, 127.7, 127.8, 127.9, 127.9, 127.9, 128.0, 128.2, 128.2, 128.3, 128.4, 128.5, 128.5, 128.6 (15 x d, 15 x Ar-$\underline{C}$), 136.7, 136.8, 136.9, 137.4, 137.7, 137.9 (6 x s, 6 x Ar-$\underline{C}$); HRMS (ESI) calculated for $C_{36}H_{51}N_2O_6S$ 639.3468. Found 639.3469 (MH^+).

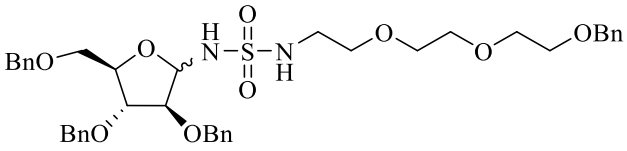
_N_-(2-(2-(Benzyloxy)ethoxy)ethyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20k



General procedure C, using sulfamide **2.19k**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.2), afforded glycosylsulfamide **2.20k** (0.36 g, 74 %, α:β, 1:1) as a yellow waxy solid. υ_{max} (neat) 3267 (N-H), 1348 (s, S=O), 1074 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 3.18-3.27 (2H, m, NHC$\underline{H}_2$), 3.47-3.49 (1H, m, H-5), 3.55-3.63 (7H, m, 3 x CH_2, H-5'), 3.93-3.97 (1H, m, H-3), 4.01 (1H, at, *J* 3.5 Hz, H-2), 4.36 (1H, t, *J* 5.5 Hz, H-4), 4.45-4.56 (8H, m, PhC$\underline{H}_2$), 5.40 (1H, d, $J_{1,NH}$ 10.2 Hz, H-1), 5.78 (1H, d, $J_{NH,1}$ 10.6 Hz, NH), 7.22-7.36 (20H, m,

Ar-H); β anomer: 3.18-3.27 (2H, m, NHC$\underline{H}_2$), 3.52 (2H, d, *J* 5.5 Hz, H-5, H-5'), 3.55-3.63 (6H, m, 3 x CH_2), 3.93-3.97 (1H, m, H-3), 3.99 (1H, at, *J* 4.3 Hz, H-2), 4.03-4.05 (1H, m, H-4), 4.45-4.56 (8H, m, PhC$\underline{H}_2$), 5.36 (1H, dd, $J_{1,2}$ 4.3 Hz, $J_{NH,1}$ 10.2 Hz, H-1), 5.62 (1H, d, $J_{NH,1}$ 10.2 Hz, NH), 7.22-7.36 (20H, m, Ar-H); δ_C (100.5 MHz, $CDCl_3$) 43.1, 43.3 (2 x t, NH$\underline{C}H_2$α, NH$\underline{C}H_2$β), 69.3, 69.6, 69.7 (3 x t, 3x CH_2), 70.1, 70.2 (2 x t, C-5α, C-5β), 71.7, 71.8, 71.9, 72.3,73.2, 73.2, 73.3, 73.4 (8 x t, 8 x Ph$\underline{C}H_2$), 80.7 (d, C-4β), 81.2, 81.8 (2 x d, C-2α, C-2β), 82.4 (d, C-3β), 82.6 (d, C-4α), 84.2 (d, C-1β), 85.2 (d, C-3α), 88.3 (d, C-1α), 127.7, 127.7, 127.7, 127.8, 127.8, 127.8, 127.9, 128.0, 128.1, 128.2, 128.2, 128.4, 128.4, 128.5, 128.5, 128.5, 128.6, 128.6 (18 x d, Ar-$\underline{C}$), 136.8, 136.9, 137.0, 137.5, 137.7, 137.9, 137.9, 138.0 (8 x s, Ar-$\underline{C}$); HRMS (ESI) calculated for $C_{37}H_{44}N_2NaO_8S$ 699.2716. Found 699.2714 (MNa^+).

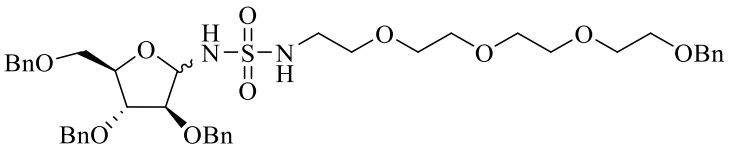
_N_-2-(2-(2-(Benzyloxy)ethoxy)ethoxy)ethyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20l



General procedure C, sulfamide **2.19l**, and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.2), afforded glycosylsulfamide **2.20l** (0.29 g, 83 %, α:β, 1.1) as a yellow waxy solid. υ_{max} (neat) 3262 (N-H), 1343 (s, S=O), 1068(s, S=O) cm^{-1} δ_H (400 MHz, $CDCl_3$) α anomer: 3.18-3.22 (2H, m, NHC$\underline{H}_2$), 3.48 (1H, dd, *J* 9.6 Hz, *J* 7.2 Hz, H-5), 3.55-3.65 (11H, m, 5 x CH_2, H-5'), 3.93-3.97 (1H, m, H-3), 4.00 (1H, at, *J* 2.7 Hz, H-2), 4.36 (1H, t, *J* 6.6 Hz, H-4), 4.41-4.58 (8H, m, PhC$\underline{H}_2$), 5.41 (1H, d,

$J_{1,NH}$ 8.6 Hz, H-1), 5.72 (1H, d, $J_{NH,1}$ 10.2 Hz, NH) , 7.22-7.35 (20H, m, Ar-H); β anomer: 3.18-3.22 (2H, m, NHC$\underline{H}_2$), 3.52 (2H, d, *J* 5.5 Hz, H-5, H-5'), 3.55-3.65 (10H, m, 5 x CH_2), 3.93-3.97 (1H, m, H-3), 3.98 (1H, at, *J* 3.5 Hz, H-2), 4.01-4.05 (1H, m, H-4), 4.41-4.58 (8H, m, $PhCH_2$), 5.36 (1H, dd, $J_{1,2}$ 4.5 Hz, $J_{NH,1}$ 10.0 Hz, H-1), 5.62 (1H, d, $J_{NH,1}$ 9.8 Hz, NH), 7.22-7.35 (20H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 43.0, 43.1 (2 x t, $NHCH_2\alpha$, $NHCH_2\beta$), 69.4, 69.4, 69.5, 70.0, 70.1 (5 x t, 5 x CH_2), 70.5, 70.6 (2 x t, C-5α, C-5β), 71.6, 71.7, 71.8, 71.9, 72.2, 73.1, 73.3, 73.4 (8 x t, 8 x $PhCH_2$), 80.6 (d, C-4β), 81.2, 81.8 (2 x d, C-2α, C-2β), 82.4 (d, C-3β), 82.6 (d, C-4α), 84.2 (d, C-1β), 85.2 (d, C-3α), 88.3 (d, C-1α), 127.6, 127.7, 127.7, 127.8, 127.8, 127.8, 127.9, 127.9, 128.0, 128.1, 128.2, 128.2, 128.4, 128.4, 128.5, 128.5, 128.6, 128.6 (18 x d, Ar-$\underline{C}$), 136.8, 136.9, 137.0, 137.5, 137.7, 138.0, 138.2, 138.2 (8 x s, Ar-$\underline{C}$); HRMS (ESI) calculated for $C_{39}H_{48}N_2NaO_9S$ 743.2978. Found 743.2980 (MNa^+).

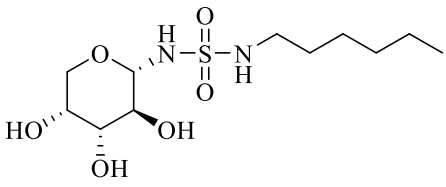
_N_-2-(2-(2-(2-(Benzyloxy)ethoxy)ethoxy)ethoxy)ethyl)-_N_'-(2,3,5-tri-_O_-benzyl-α,β-D-arabinofuranosyl)sulfamide 2.20m



General procedure C, using sulfamide **2.19m**, and purification by flash chromatography (petrol: EtOAc, 1:1, R_f 0.2), afforded glycosylsulfamide **2.20m** (0.23 g, 62 %, α:β, 1:1) as a yellow oil. υ_{max} (neat) 3254 (N-H), 1346 (s, S=O), 1089 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 3.19-3.23 (2H, m, NHC$\underline{H}_2$), 3.48 (1H, m, H-5), 3.55-3.65 (15H, m, 7 x CH_2, H-5'), 3.93-3.97 (1H, m, H-3), 3.99 (1H, at, *J* 2.0 Hz, H-2), 4.36 (1H, t, *J* 6.2 Hz, H-4), 4.42-4.59 (8H, m, $PhCH_2$), 5.41 (1H, d,

$J_{NH,1}$ 9.8 Hz, H-1), 5.73 (1H, d, $J_{NH,1}$ 10.9 Hz, NH), 7.23-7.35 (20H, m, Ar-H); β anomer: 3.19-3.23 (2H, m, $NHCH_2$), 3.52 (2H, d, *J* 5.1 Hz, H-5, H-5'), 3.55-3.65 (14H, m, 7 x CH_2), 3.93-3.97 (1H, m, H-3), 4.01 (1H, at, *J* 3.5 Hz, H-2), 4.03-4.05 (1H, m, H-4), 4.42-4.59 (8H, m, $PhCH_2$), 5.37 (1H, dd, $J_{1,2}$ 4.5 Hz, $J_{NH,1}$ 10.4 Hz, H-1), 5.63 (1H, d, $J_{NH,1}$ 10.2 Hz, NH), 7.23-7.35 (20H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 43.0, 43.1 (2 x t, $NHCH_2\alpha$, $NHCH_2\beta$), 69.4, 69.5, 69.5, 70.0, 70.1, 70.1, 70.2 (7 x t, 7x CH_2), 70.5, 70.6 (2 x t, C-5α, C-5β), 71.7, 71.8, 71.9, 72.3, 73.2, 73.2, 73.3, 73.4 (8 x t, 8 x $PhCH_2$), 80.6 (d, C-4β), 81.3, 81.8 (2 x d, C-2α, C-2β), 82.5 (d, C-3β), 82.6 (d, C-4α), 84.2 (d, C-1β), 85.2 (d, C-3α), 88.2 (d, C-1α), 127.6, 127.7, 127.7, 127.8, 127.8, 127.8, 127.9, 127.9, 128.1, 128.2, 128.2, 128.3, 128.4, 128.5, 128.5, 128.5, 128.6, 128.6 (18 x d, Ar-C), 136.8, 136.9, 137.0, 137.5, 137.7, 138.0, 138.2, 138.2 (8 x s, Ar-C); HRMS (ESI) calculated for $C_{41}H_{52}N_2NaO_{10}S$ 787.3240. Found 787.3247 (MNa^+).

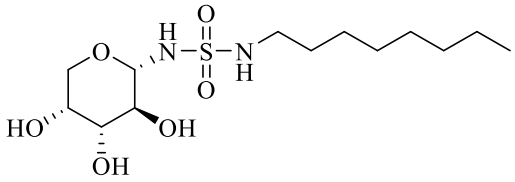
***N*-(Hexyl)-*N'*-(α-D-arabinopyranosyl)sulfamide 2.21a**



General Procedure F, using sulfamide **2.20a**, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 35-85 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21a** (18 mg, 42 %) as white solid. $[\alpha]_D^{20}$ -11.6 (*c*, 0.5 in CH_3OH); m.p 125-128 °C ($MeOH/Et_2O$); υ_{max} (neat) 3310 (br, OH), 1318 (s, S=O), 1134 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 0.92 (3H, t, *J* 7.3 Hz,

C<u>H</u>$_3$), 1.28-1.38 (6H, m, 3 x C<u>H</u>$_2$), 1.48-1.54 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.93-3.01 (2H, m, C<u>H</u>$_2$NH), 3.46 (1H, at, *J* 8.3 Hz, H-2), 3.51-3.56 (2H, m, H-3, H-5), 3.77-3.82 (2H, m, H-4, H-5'), 4.27 (1H, at, $J_{1,2}$ 8.9 Hz, H-1), 5.07-5.13 (1H, m, N<u>H</u>CH$_2$), 6.12 (1H, d, $J_{1,NH}$ 9.8 Hz, N<u>H</u>SO$_2$); δ_C (100.5 MHz, CD$_3$OD) 12.9 (q, CH$_3$), 22.2, 26.2, 29.1, 31.2 (4 x t, 4 x CH$_2$), 42.6 (t, CH$_2$NH), 66.7 (t, C-5), 68.3 (d, C-4), 70.0 (d, C-2), 73.5 (d, C-3), 85.1 (d, C-1); HRMS (ESI) calculated for $C_{11}H_{24}N_2NaO_6S$ 335.1253. Found 335.1246 (MNa^+).

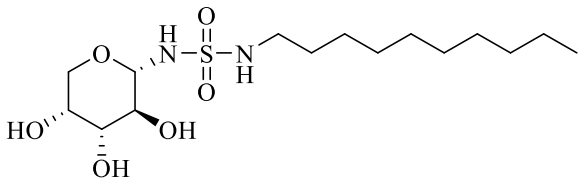
_N_-(Octyl)-_N'_-(α-D-arabinopyranosyl)sulfamide 2.21b



General Procedure F, using sulfamide **2.20b**, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H$_2$O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 35-85 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21b** (16 mg, 36 %) as white solid. $[\alpha]_D^{20}$ -15.6 (*c*, 0.5 in MeOH); m.p 115-118 °C (MeOH/Et$_2$O); υ_{max} (neat) 3315 (br, OH), 1316 (s, S=O), 1152 (s, S=O) cm^{-1}; δ_H (400 MHz, CD$_3$CN) 0.91 (3H, t, *J* 6.7 Hz, C<u>H</u>$_3$), 1.29-1.36 (10H, m, 5 x C<u>H</u>$_2$), 1.48-1.54 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.93-3.00 (2H, m, C<u>H</u>$_2$NH), 3.45 (1H, at, *J* 8.3 Hz, H-2), 3.51-3.54 (1H, m, H-3), 3.55-3.56 (1H, m, H-5), 3.78-3.80 (1H, m, H-4), 3.81 (1H, d, *J* 2.9 Hz, H-5'), 4.27 (1H, at, $J_{1,2}$ 8.1 Hz, H-1), 5.07-5.13 (1H, m, N<u>H</u>CH$_2$); δ_C (100.5 MHz, CD$_3$OD) 13.0 (q, CH$_3$), 22.3, 26.5, 28.8, 29.0, 29.1, 31.8 (6 x t, 6 x CH$_2$), 42.6 (t, CH$_2$NH), 66.7 (t, C-5), 68.3 (d, C-4),

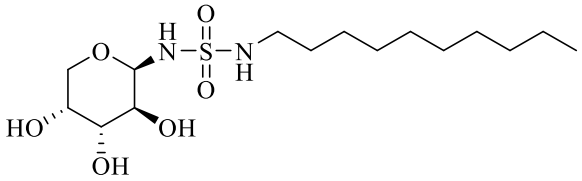
70.0 (d, C-2), 73.5 (d, C-3), 85.1 (d, C-1); HRMS (ESI) calculated for $C_{13}H_{28}N_2NaO_6S$ 363.1566. Found 363.1570 (MNa^+).

***N*-(Decyl)-*N'*-(α-D-arabinopyranosyl)sulfamide 2.21c**



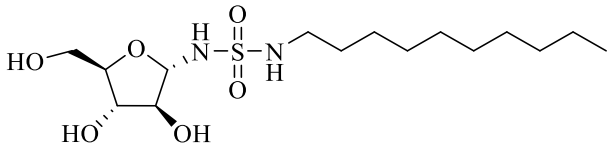
General Procedure F, using sulfamide **2.20c** and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21c** (21 mg, 45 %) as white solid; $[\alpha]_D^{20}$ -14 (*c*, 0.5 in CH_3OH); m.p. 103-105 °C (MeOH/Et_2O); υ_{max} (neat) 3340 (br, OH), 1340 (s, S=O), 1157 (s, S=O) cm^{-1}; δ_H (500 MHz, CD_3CN) 0.90 (3H, t, *J* 6.7 Hz, C<u>H</u>$_3$), 1.29-1.36 (14H, m, 7 x C<u>H</u>$_2$), 1.49-1.53 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.95-2.99 (2H, t, C<u>H</u>$_2$NH), 3.44 (1H, at, *J* 7.3 Hz, H-2), 3.53-3.56 (2H, m, H-3, H-5), 3.77-3.80 (1H, m, H-4), 3.84 (1H, d, $J_{4,5'}$ 4.0 Hz, H-5'), 4.27 (1H, d, $J_{1,2}$ 7.6 Hz, H-1), 5.03 (1H, t, *J* 5.8 Hz, N<u>H</u>CH$_2$); δ_C (100.5 MHz, CD_3OD) 13.0 (q, CH_3), 22.3, 26.5, 29.0, 29.3, 31.6 (5 x t, 8 x CH_2), 42.6 (t, <u>C</u>H$_2$NH), 66.7 (t, C-5), 68.3 (d, C-4), 70.0 (d, C-2), 73.5 (d, C-3), 85.1 (d, C-1); HRMS (ESI) calculated for $C_{15}H_{32}N_2NaO_6S$ 391.1879. Found 391.1881 (MNa^+).

***N*-(Decyl)-*N'*-(β-D-arabinopyranosyl)sulfamide 2.22a**



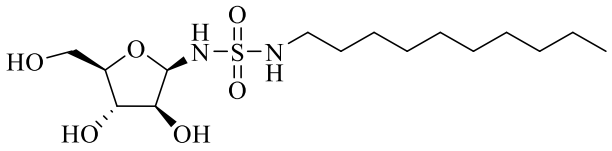
δH (400 MHz, CD_3CN) 0.91 (3H, t, *J* 6.7 Hz, CH_3), 1.25-1.40 (14H, m, 7 x CH_2), 1.45-1.56 (2H, m, $NHCH_2C\underline{H}_2$), 2.93-3.00 (2H, t, CH_2NH), 3.53 (1H, dd, $J_{5,5'}$ 11.0 Hz, $J_{4,5'}$ 9.0 Hz, H-5), 3.66 (1H, dd, $J_{5,5'}$ 11.6 Hz, $J_{4,5'}$ 4.3 Hz, H-5'), 3.70 (1H, dd, $J_{2,3}$ 5.5 Hz, $J_{1,2}$ 2.3 Hz H-2), 3.78-3.80 (1H, m, H-3), 3.86-3.89 (1H, m, H-4), 4.84 (1H, d, $J_{1,NH}$ 9.0 Hz, H-1), 5.06 (1H, t, *J* 4.6 Hz, $NHCH_2$), 5.73 (1H, d, $J_{1,NH}$ 9.8 Hz, NH-1); δC (100 MHz, CD_3CN) 13.4 (q, CH_3), 22.4, 26.5, 28.9, 29.0, 29.3, 31.6 (6 x t, 8 x CH_2), 42.9 (t, CH_2NH), 63.9 (t, C-5), 64.1 (d, C-4), 69.9 (d, C-2), 70.0 (d, C-3), 80.2 (d, C-1).

***N*-(Decyl)-*N'*-(α-D-arabinofuranosyl)sulfamide 2.22b**



δH (400 MHz, CD_3CN) 0.91 (3H, t, *J* 6.7 Hz, CH_3), 1.25-1.40 (14H, m, 7 x CH_2), 1.45-1.56 (2H, m, $NHCH_2C\underline{H}_2$), 2.93-3.00 (2H, t, CH_2NH), 3.60-3.65 (2H, m, H-5, H-5'), 3.76 (1H, at, *J* 2.8 Hz, H-3), 3.89-3.95 (1H, m, H-2), 3.97-3.99 (1H, m, H-4), 4.95 (1H, dd, $J_{1,NH}$ 10.6 Hz, $J_{1,2}$ 2.7 Hz, H-1), 5.00 (1H, t, *J* 4.6 Hz, $NHCH_2$), 5.98 (1H, d, $J_{1,NH}$ 11.2 Hz, NH-1).

***N*-(Decyl)-*N'*-(β-D-arabinofuranosyl)sulfamide 2.22c**

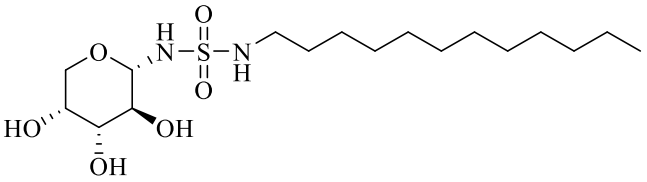


δH (400 MHz, CD_3CN) 0.91 (3H, t, *J* 6.7 Hz, CH_3), 1.25-1.40 (14H, m, 7 x CH_2), 1.45-1.56 (2H, m, $NHCH_2C\underline{H}_2$), 2.93-3.00 (2H, t, CH_2NH), 3.60-3.65 (2H, m, H-5, H-5'), 3.68 (1H, at, *J* 2.8 Hz, H-3), 3.84 (1H, at, *J* 2.9 Hz, H-2), 4.02 (1H, aq, *J* 4,7 Hz, H-4), 5.13 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 5.00 (1H, t, *J* 4.6 Hz, $NHCH_2$).

Experimental Procedure for time dependent isomerization studies of glycosyl sulfamides 2.21c and 2.22a-c

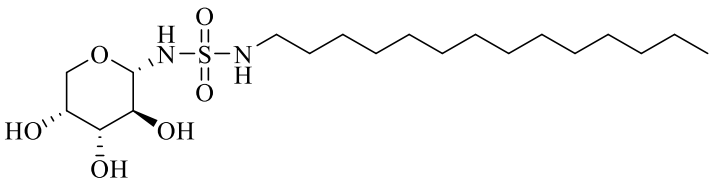
The debenzylated glycosyl sulfamide (10 mg, 0.03 mmol) was dissolved in methanol (1 mL), and purified by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD). Each of the three peaks **(Figure 2.5)** were separated and frozen immediately. After freeze drying, the samples (1 mg, 0.003 mmol) were then dissolved in a mixture of H_2O and MeOH (4:1), and the equilibration of the three samples was analysed by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD) over a 48 hour time period. The results are shown in **Figure 2.8, 2.9 and 2.10**.

***N*-(Dodecyl)-*N'*-(α-D-arabinopyranosyl)sulfamide 2.21d**



General Procedure F, using sulfamide **2.20d**, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21d** (19 mg, 40 %) as white solid. $[\alpha]_D^{20}$ -12.3 (*c*, 0.5 in CH_3OH); m.p 108-110 °C (MeOH/Et_2O); υ_{max} (neat) 3320 (br, OH), 1330 (s, S=O), 1154 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 0.91 (3H, t, *J* 7.3 Hz, C<u>H</u>$_3$), 1.27-1.36 (18H, m, 9 x C<u>H</u>$_2$), 1.47-1.54 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.94-3.00 (2H, m, C<u>H</u>$_2$NH), 3.45 (1H, at, *J* 8.0 Hz, H-2), 3.52-3.54 (1H, m, H-3), 3.54-3.56 (1H, m, H-5), 3.77-3.80 (1H, m, H-4), 3.80-3.82 (1H, m, H-5'), 4.27 (1H, d, $J_{1,2}$ 7.3 Hz, H-1), 5.04 (1H, t, *J* 6.6 Hz, N<u>H</u>CH$_2$); δ_C (100.5 MHz, CD_3OD) 13.0 (q, CH_3), 22.3, 26.5, 29.0, 29.0, 29.1, 29.3, 29.3, 29.3, 29.4, 31.6 (10 x t, 10 x CH_2), 42.6 (t, CH_2NH), 66.7 (t, C-5), 68.3 (d, C-4), 70.0 (d, C-2), 73.5 (d, C-3), 85.1 (d, C-1); HRMS (ESI) calculated for $C_{17}H_{36}N_2NaO_6S$ 419.2192. Found 419.2201 (MNa^+).

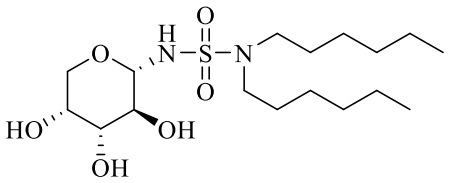
***N*-(Tetradecyl)-*N'*-(α-D-arabinopyranosyl)sulfamide 2.21e**



General Procedure F, using sulfamide **2.20e**, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient:

the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21e** (23mg, 47 %) as white solid. $[\alpha]_D^{20}$ -11.4 (*c*, 0.5 in MeOH); m.p 118-128 °C (MeOH/Et_2O); υ_{max} (neat) 3410 (br, OH), 1325 (s, S=O), 1149 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 0.91 (3H, t, *J* 6.5 Hz, C<u>H</u>$_3$), 1.27-1.37 (22H, m, 11 x C<u>H</u>$_2$), 1.49-1.52 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.94-3.00 (2H, m, C<u>H</u>$_2$NH),), 3.45 (1H, at, *J* 8.3 Hz, H-2), 3.51-3.54 (1H, m, H-3), 3.54-3.56 (1H, m, H-5), 3.77-3.80 (1H, m, H-4), 3.80-3.82 (1H, m, H-5'), 4.27 (1H, d, $J_{1,2}$ 7.8 Hz, H-1), 5.02-5.07 (1H, m, N<u>H</u>CH$_2$); δ_C (100.5 MHz, CD_3OD) 13.0 (q, CH_3), 22.3, 26.5, 29.0, 29.0, 29.1, 29.3, 29.3, 29.3, 29.4, 31.6 (10 x t, 12 x CH_2), 42.6 (t, CH_2NH), 66.7 (t, C-5), 68.3 (d, C-4), 70.0 (d, C-2), 73.5 (d, C-3), 85.1 (d, C-1); HRMS (ESI) calculated for $C_{19}H_{41}N_2O_6S$ 425.2685. Found 425.2699 (MNa^+).

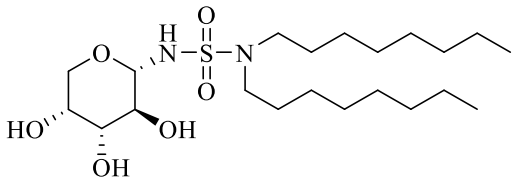
***N,N-(*Dihexyl)-*N'*-(α-D-arabinopyranosyl)sulfamide 2.21f**



General Procedure F, using sulfamide **2.20f**, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21f** (12 mg, 41 %) as yellow waxy solid. $[\alpha]_D^{20}$ -12.1 (*c*, 0.5 in MeOH); υ_{max} (neat) 3366 (br, OH), 1334 (s, S=O), 1135 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 0.92 (6H, t, *J* 6.5 Hz, 2 x C<u>H</u>$_3$), 1.29-1.37 (12H, m, 6 x C<u>H</u>$_2$), 1.53-1.62 (4H, m, 2 x NHCH$_2$C<u>H</u>$_2$), 3.03-3.15 (4H, t, 2 x C<u>H</u>$_2$NH), 3.43 (1H, at, *J* 8.3 Hz, H-2), 3.50-3.55 (2H, m, H-3, H-5), 3.77-3.79 (1H, m,

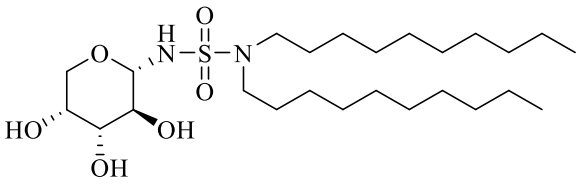
H-4), 3.80-3.82 (1H, m, H-5'), 4.24 (1H, d, $J_{1,2}$ 7.8 Hz, H-1); δ_C (100.5 MHz, CD_3OD) 12.9 (q, 2 x CH_3), 22.3, 26.2, 28.8, 31.3 (4 x t, 8 x CH_2), 49.1 (t, 2 x CH_2NH), 66.4 (t, C-5), 68.2 (d, C-4), 70.1 (d, C-2), 73.5 (d, C-3), 85.0 (d, C-1); HRMS (ESI) calculated for $C_{17}H_{37}N_2O_6S$ 397.2372. Found 397.2380 (MH^+).

***N,N-(*Dioctyl)-*N'*-(α-D-arabinopyranosyl)sulfamide 2.21g**



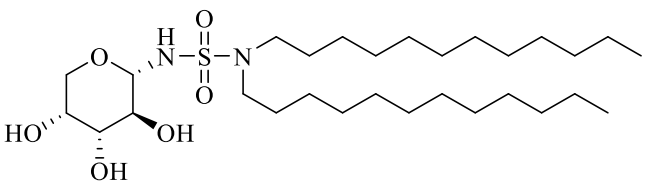
General Procedure F, using sulfamide **2.20g**, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21g** (14 mg, 45 %) as yellow waxy solid. $[\alpha]_D^{20}$ -14.8 (*c*, 0.5 in MeOH); υ_{max} (neat) 3396 (br, OH), 1313 (s, S=O), 1140 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 0.91 (6H, t, *J* 6.2 Hz, 2 x C<u>H</u>$_3$), 1.26-1.37 (20H, m, 10 x C<u>H</u>$_2$), 1.54-1.61 (4H, m, 2 x NHCH$_2$C<u>H</u>$_2$), 3.02-3.14 (4H, m, 2 x C<u>H</u>$_2$NH), 3.43 (1H, at, *J* 8.1 Hz, H-2), 3.49-3.55 (2H, m, H-3, H-5), 3.75-3.80 (2H, m, H-4, H-5'), 4.24 (1H, d, $J_{1,2}$ 7.6 Hz, H-1); δ_C (100.5 MHz, CD_3OD) 13.0 (q, 2 x CH_3), 22.3, 26.5, 28.8, 28.9, 28.9, 31.5 (6 x t, 12 x CH_2), 49.1 (t, 2 x CH_2NH), 66.4 (t, C-5), 68.2 (d, C-4), 70.1 (d, C-2), 73.5 (d, C-3), 85.1 (d, C-1); HRMS (ESI) calculated for $C_{21}H_{45}N_2O_6S$ 453.2998. Found 453.3007 (MH^+).

***N,N-(*Didecyl)-*N'*-(α-D-arabinopyranosyl)sulfamide 2.21h**



General Procedure F, using sulfamide **2.20h**, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21h** (16 mg, 41 %) as yellow waxy solid. $[\alpha]_D^{20}$ -13.2 (*c*, 0.5 in MeOH); υ_{max} (neat) 3389 (w, NH), 1337 (s, S=O), 1137 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 0.91 (6H, t, *J* 6.5 Hz, 2 x C<u>H</u>$_3$), 1.27-1.37 (28H, m, 14 x C<u>H</u>$_2$), 1.54-1.61 (4H, m, 2 x NHCH$_2$C<u>H</u>$_2$), 3.04-3.15 (4H, t, 2 x C<u>H</u>$_2$NH), 3.44 (1H, at, *J* 8.1 Hz, H-2), 3.50-3.57 (2H, m, H-3, H-5), 3.77-3.82 (2H, m, H-4, H-5'), 4.26 (1H, at, *J* 9.0 Hz, H-1), 5.96 (1H, d, $J_{1,NH}$ 9.8 Hz, N<u>H</u>SO$_2$); δ_C (100.5 MHz, CD_3OD) 13.0 (q, 2 x CH_3), 22.3, 26.4, 28.8, 28.9, 29.0, 29.3, 29.3, 31.6 (8 x t, 16 x CH_2), 49.1 (t, 2 x CH_2NH), 66.4 (t, C-5), 68.2 (d, C-4), 70.1 (d, C-2), 73.5 (d, C-3), 85.1 (d, C-1); HRMS (ESI) calculated for $C_{25}H_{53}N_2O_6S$ 509.3624. Found 509.3634 (MH^+).

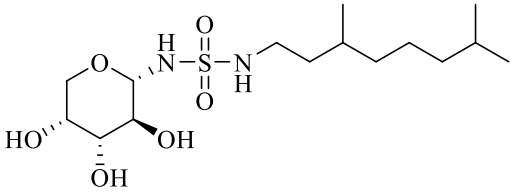
***N,N-(*Didodecyl)-*N'*-(α-D-arabinopyranosyl)sulfamide 2.21i**



General Procedure F, using sulfamide **2.20i**, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient:

the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21i** (13 mg, 39 %) as yellow waxy solid. $[\alpha]_D^{20}$ -15.2 (*c*, 0.5 in MeOH); υ_{max} (neat) 3385 (br, OH), 1315 (s, S=O), 1132 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 0.91 (6H, t, *J* 6.5 Hz, 2 x C<u>H</u>$_3$), 1.27-1.37 (36H, m, 18 x C<u>H</u>$_2$), 1.54-1.61 (4H, m, 2 x NHCH$_2$C<u>H</u>$_2$), 3.04-3.15 (4H, t, 2 x C<u>H</u>$_2$NH), 3.44 (1H, at, *J* 8.1 Hz, H-2), 3.50-3.57 (2H, m, H-3, H-5), 3.77-3.82 (2H, m, H-4, H-5'), 4.26 (1H, at, *J* 9.0 Hz, H-1), 5.96 (1H, d, $J_{1,NH}$ 9.8 Hz, N<u>H</u>SO$_2$); δ_C (100.5 MHz, CD_3OD) 13.0 (q, 2 x CH_3), 22.3, 26.4, 28.8, 29.0, 29.1, 29.2, 29.3, 29.3, 29.4, 31.6 (10 x t, 20 x CH_2), 49.1 (t, 2 x CH_2NH), 66.4 (t, C-5), 68.2 (d, C-4), 70.1 (d, C-2), 73.5 (d, C-3), 85.1 (d, C-1); HRMS (ESI) calculated for $C_{29}H_{61}N_2O_6S$ 565.4250. Found 565.4255 (MH^+)

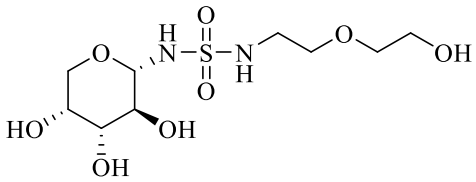
***N*-(3,7-Dimethyloctyl)-*N'*-(α-D-arabinopyranosyl)sulfamide 2.21j**



General Procedure F, using sulfamide **2.20j**, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21j** (10 mg, 43 %) as yellow waxy solid. $[\alpha]_D^{20}$ -11.2 (*c*, 0.5 in MeOH); υ_{max} (neat) 3391 (br, OH), 1314 (s, S=O), 1134 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 0.88-0.91 (9H, m, 3 x CH_3), 1.16-1.21 (2H, m, CH_2), 1.32-1.36 (6H, m, 3 x CH_2), 1.54-1.59 (2H, m, 2 x CH), 2.98-3.05 (2H, m, C<u>H</u>$_2$NH), 3.44 (1H, at, *J* 8.1 Hz, H-2), 3.50-3.57 (2H, m, H-3, H-5), 3.76-3.86 (2H,

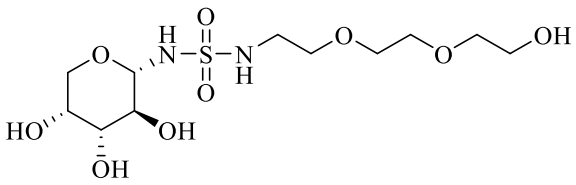
m, H-4, H-5'), 4.27 (1H, at, *J* 9.0 Hz, H-1), 5.00-5.02 (1H, m, N<u>H</u>CH_2), 6.11 (1H, d, $J_{1,NH}$ 10.2 Hz, N<u>H</u>SO_2); δ_C (100.5 MHz, CD_3OD) 18.4, 22.5, 22.6 (3 x q, 3 x <u>C</u>H_3), 24.4 (t, <u>C</u>H_2), 27.7, 30.2 (2 x d, 2 x <u>C</u>H), 36.2 (t, <u>C</u>H_2), 36.9 (t, <u>C</u>H_2), 39.0 (t, <u>C</u>H_2CH_2NH), 40.7 (t, <u>C</u>H_2NH), 66.7 (t, C-5), 68.3 (d, C-4), 70.1 (d, C-2), 73.5 (d, C-3), 85.1 (d, C-1); HRMS (ESI) calculated for $C_{15}H_{32}N_2NaO_6S$ 391.1879. Found 391.1887 (MNa^+).

_N_-(2-(2-ethoxy)ethanol-_N_'-(α-D-arabinopyranosyl)sulfamide 2.21k



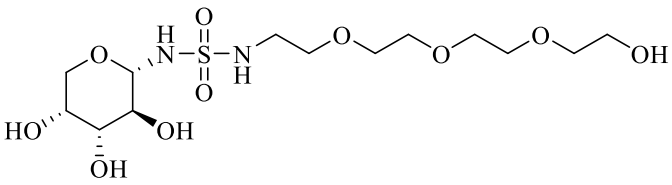
General Procedure F, using sulfamide **2.20k**, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 10-35 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21k** (6 mg, 46 %) as yellow waxy solid. . $[\alpha]_D^{20}$ -11.7 (*c*, 0.5 in MeOH); υ_{max} (neat) 3328 (br, OH), 1324 (s, S=O), 1130 (s, S=O) cm^{-1}; δ_H (500 MHz, CD_3OD) 3.19-3.24 (2H, m, NHC<u>H</u>$_2$), 3.52-3.56 (4H, m, CH_2, H-2, H-3), 3.58 (1H, m, H-5), 3.60 (2H, m, CH_2), 3.67 (2H, t, *J* 5.0 Hz, CH_2), 3.82-3.84 (1H, m, H-4), 3.85-3.87 (1H, m, H-5'), 4.32 (1H, d, $J_{1,2}$ 7.8 Hz, H-1); δ_C (125 MHz, CD_3OD) 42.4 (t, <u>C</u>H_2NH), 60.8 (t, CH_2), 66.8 (t, C-5), 68.3 (d, C-4), 69.4 (t, CH_2), 70.0 (d, C-2), 71.9 (t, CH_2), 73.5 (d, C-3), 85.2 (d, C-1); HRMS (ESI) calculated for $C_9H_{20}N_2NaO_8S$ 339.0838. Found 339.0830 (MNa^+).

***N*-(2-(2-(2-(ethoxy)ethoxy)ethanol-*N*'-(α-D-arabinopyranosyl)sulfamide 2.21l**



General Procedure F, using sulfamide **2.20l,** and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 10-35 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21l** (6 mg, 42 %) as yellow waxy solid. $[\alpha]_D^{20}$ -12.4 (*c*, 0.5 in MeOH); υ_{max} (neat) 3330 (br, OH), 1322 (s, S=O), 1131 (s, S=O) cm^{-1}; δ_H (500 MHz, CD_3OD) 3.19-3.24 (2H, m, NHC$\underline{H}_2$), 3.53-3.56 (2H, m, H-2, H-3), 3.57-3.59 (3H, m, CH_2, H-5), 3.60-3.63 (2H, m, CH_2), 3.64-3.68 (4H, m, 2 x CH_2), 3.68- 3.70 (2H, m, CH_2), 3.83-3.86 (2H, m, H-4, H-5'), 4.33 (1H, t, $J_{1,2}$ 7.6 Hz, H-1); δ_C (125 MHz, CD_3OD) 42.4 (t, CH_2NH), 60.7 (t, CH_2), 66.8 (t, C-5), 68.3 (d, C-4), 69.5, 69.7, 69.9 (3 x t, 3 x CH_2), 70.1 (d, C-2), 72.3 (t, CH_2), 73.5 (d, C-3), 85.3 (d, C-1); HRMS (ESI) calculated for $C_{11}H_{24}N_2NaO_9S$ 383.1100. Found 383.1105 (MNa^+).

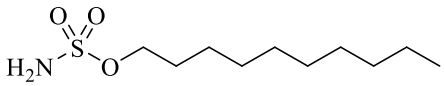
***N*-(2-(2-(2-(2-ethoxy)ethoxy)ethoxy)ethyl)ethanol-*N*'-(β-D-arabinopyranosyl)sulfamide 2.21m**



General Procedure F, using sulfamide **2.20m,** and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient:

the sample was run at 1 mL/min with a gradient of 10-35 % B; column oven: 15 °C; detection: CAD), afforded de-protected sulfamide **2.21m** (7 mg, 46 %) as yellow waxy solid. $[\alpha]_D^{20}$ -10.6 (*c*, 0.5 in MeOH); υ_{max} (neat) 3324 (br, OH), 1326 (s, S=O), 1131 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3OD) 3.12-3.24 (2H, m, NHC$\underline{H}_2$), 3.55-3.68 (17H, m, 7 x CH_2, H-2, H-3, H-5), 3.83-3.86 (2H, m, H-4, H-5'), 4.32 (1H, d, $J_{1,2}$ 7.0 Hz, H-1); δ_C (100.5 MHz, CD_3OD) 42.4 (t, CH_2NH), 60.8 (t, CH_2), 66.8 (t, C-5), 68.3 (d, C-4), 69.5, 69.6, 69.7, 69.9 (4 x t, 4 x CH_2), 70.0 (d, C-2), 72.0, 72.1 (2 x t, 2 x CH_2), 73.5 (d, C-3), 85.2 (d, C-1); HRMS (ESI) calculated for $C_{13}H_{28}N_2NaO_{10}S$ 427.1362. Found 427.1365 (MNa^+).

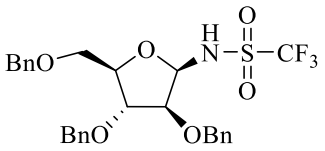
_n_-Decyl sulfamate 2.24[139]



n-Decanol **2.23** (250 mg, 1.5 mmol), and sulfamoyl chloride (300 mg, 2 equiv.) were added to *N*,*N*-dimethylacetamide at 0 °C under nitrogen. The reaction was allowed to warm to room temperature and then stirred for 3 hours. After this time, t.l.c. (Petrol: EtOAc, 3:1) indicated the formation of a single product (R_f 0.1), and the complete consumption of starting material (R_f 0.0). The reaction mixture was then poured into cold brine (20 mL), and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue which was purified by flash chromatography (petrol: ethyl acetate, 3:1) to afford n-decyl sulfamate **2.24** (380 mg, 85 %) as a white crystalline solid. mp 72-75 °C (DCM/Petrol) (lit.[139] 69-71 °C); υ_{max} (neat) 3367 (w, N-H), 3285

(m, N-H), 1343 (s, S=O), 1177 (s, S=O) cm^{-1}; δ_H (400 MHz, DMSO) 0.84 (3H, t, *J* 6.4 Hz, C$\underline{H}_3$), 1.23-1.29 (14H, m, 7 x C$\underline{H}_2$), 1.59 (2H, t, *J* 6.8 Hz, OCH$_2$C$\underline{H}_2$), 3.98 (2H, t, *J* 6.4 Hz, C$\underline{H}_2$O), 7.35 (2H, s, N$\underline{H}_2$); δ_C (100 MHz, DMSO) 14.4 (q, $\underline{C}H_3$), 22.5, 25.5, 28.7, 28.9, 29.1, 29.4, 31.7 (7 x t, 8 x $\underline{C}H_2$), 69.4 (t, $\underline{C}H_2O$); HRMS (ESI) calculated for $C_{10}H_{23}NNaO_3S$ 260.1296. Found 260.1282 (MNa^+).

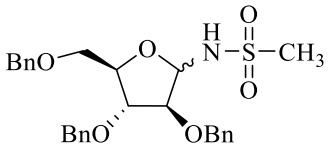
1,1,1-Trifluoro-*N* -(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)methanesulfonamide 2.25a



2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranoside **2.6** (100 mg, 0.2 mmol), and trifluoromethanesulfonamide (71 mg, 0.3 mmol.) were stirred at room temperature in dry diethyl ether (15 mL) under nitrogen. TMSOTf (40 µl) was added dropwise, and the mixture stirred for 16 hours. After this time, t.l.c. (petrol:EtOAc, 3:1) indicated the formation of a single product (R_f 0.4), and complete consumption of starting material (R_f 0.2). The reaction mixture was then neutralized by the dropwise addition of excess triethylamine (0.1 mL), filtered through Celite®, eluting with ethyl acetate, and concentrated *in vacuo* to give a residue which was purified by flash chromatography (petrol: ethyl acetate, 3:1) to afford trifluoromethanesulfonamide **2.25a** (58 mg, 44 %) as a white solid. m.p. 110-113 °C (DCM/petrol); $[\alpha]_D^{20}$ +9.0 (*c*, 0.35 in CH_3OH); υ_{max} (neat) 3386 (w, NH), 1382 (s, S=O), 1188 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3OD) 3.59-3.62 (2H, m, H-5, H-5'), 3.90 (1H, dd, $J_{3,4}$ 6.3 Hz, $J_{2,3}$ 2.3 Hz, H-3), 4.04-4.05 (1H, m, H-2), 4.14 (1H, aq, *J* 5.5 Hz, H-4), 4.43-4.58 (6H, m, Ph-CH_2), 5.38 (1H, s,

H-1), 7.24-7.33 (15H, m, Ar-H); δ_C (100 MHz, CD_3OD) 69.6 (t, C-5), 71.5, 71.7, 72.9 (3 x t, Ph-$\underline{C}H_2$), 81.5 (d, C-4), 83.6 (d, C-3), 87.4 (d, C-2), 101.9 (d, C-1), 119.8 (q, $J_{C,F}$ 334.1 HZ, CF_3), 127.3, 127.5, 127.6, 127.9, 128.0 (5 x d, 5 x Ar-C), 137.4, 137.8, 137.9 (3 x s, 3 x Ar-C); δ_F (376.6 MHz, CD_3OD) -81.59; HRMS (ESI) calculated for $C_{27}H_{28}F_3NNaO_6S$ 574.1487. Found 574.1478 (MNa^+).

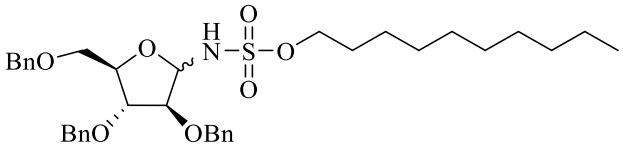
***N*-(2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranosyl)methanesulfonamide 2.25b**



2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranoside **2.6** (100 mg), and methanesulfonamide (34 mg, 0.3 mmol) were stirred at room temperature in dry DCM (15 mL) under nitrogen. TMSOTf (40 µl) was added dropwise, and the mixture stirred for 16 hours. After this time, t.l.c (petrol: ethyl acetate, 2:1) indicated the formation of a product (R_f 0.45), and the complete consumption of starting material (R_f 0.3). The reaction was then neutralized by the dropwise addition of excess triethylamine (0.1 mL). The reaction mixture was filtered through Celite®, eluting with ethyl acetate, and concentrated *in vacuo.* Purification by flash chromatography (petrol:ethyl acetate, 2:1) afforded methanesulfonamide **2.25b** (63 mg, 53 %, α:β, 2:1) as a yellow waxy solid. υ_{max} (neat) 3267 (w, NH), 1328 (s, S=O), 1159 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 3.07 (3H, s, C$\underline{H}_3$), 3.47 (1H, at, *J* 9.2 Hz, H-5), 3.58 (1H, dd, $J_{5,5'}$ 9.4 Hz, $J_{4,5'}$ 5.9 Hz, H-5'), 3.94-3.97 (1H, m, H-3), 4.02-4.05 (1H, m, H-2), 4.34 (1H, at, *J* 4.0 Hz, H-4) 4.42-4.46 (1H, m, Ph-C$\underline{H}_2$), 4.49-4.57 (5H, m, PhC$\underline{H}_2$), 5.48 (1H, d, $J_{NH,1}$ 11.0 Hz, H-1), 5.63 (1H, d, *J* 11.2 Hz, NH), 7.21-7.33 (15H, m, Ar-H); β anomer: 3.07

(3H, s, C<u>H</u>$_3$), 3.52 (2H, at, *J* 4.1 Hz, H-5, H-5'), 3.94-3.97 (1H, m, H-3), 4.02-4.05 (2H, m, H-2, H-4), 4.42-4.46 (1H, m, Ph-C<u>H</u>$_2$), 4.49-4.57(5H, m, PhC<u>H</u>$_2$), 5.42 (1H, dd, $J_{1,2}$ 4.5 Hz, $J_{NH,1}$ 10.4 Hz, H-1), 5.57 (1H, d, $J_{NH,1}$ 10.2 Hz, NH), 7.21-7.33 (15H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 42.9 (q, CH_3), 69.8, 70.1 (2 x t, C-5α, C-5β), 71.7, 71.8, 71.9, 72.3, 73.3, 73.4 (6 x t, Ph-<u>C</u>H$_2$), 80.9 (d, C-4β), 81.1 (d, C-2β), 81.9 (C-3β), 82.3 (d, , C-2α), 83.3 (d, C-4α), 83.9 (d, C-1β), 84.7 (d, C-3α), 87.9 (d, C-1α), 127.7, 127.9, 128.4, 128.5, 128.7 (5 x d, 5 x Ar-C), 136.6, 136.8, 137.9 (3 x s, 3 x Ar-C); HRMS (ESI) calculated for $C_{27}H_{31}NNaO_6S$ 520.1770. Found 520.1767 (MNa^+).

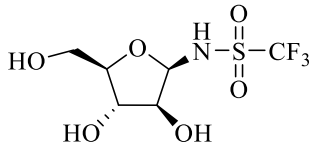
Decyl-*N*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamate 2.25c



2,3,5-Tri-*O*-benzyl-α,β-D-arabinofuranose **2.6** (100 mg, 0.2 mmol), and decyl sulfamate (68 mg, 0.3 mmol) were stirred at room temperature in dry DCM (15 mL) under nitrogen. TMSOTf (40 µl) was added dropwise, and the mixture stirred for 16 hours. After this time, t.l.c. (petrol:ethyl acetate, 3:1) indicated the formation of a single product (R_f 0.5), and the complete consumption of starting material (R_f 0.2). The reaction mixture was then neutralized by the dropwise addition of excess triethylamine (0.3 mL). The reaction mixture was filtered through Celite®, eluting with ethyl acetate, and concentrated *in vacuo* to give a residue which was purified by flash chromatography (petrol:ethyl acetate, 2:1) to afford sulfamate **2.25c** (86 mg, 56 %, α:β, 1:1) as a waxy yellow solid. υ_{max} (neat) 3280 (w, NH), 1365 (s, S=O), 1181 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.90 (3H, t, *J* 6.7 Hz, C<u>H</u>$_3$), 1.21-1.43

(14H, m, 7 x C<u>H</u>$_2$), 1.64-1.74 (2H, m, OCH$_2$C<u>H</u>$_2$), 3.44-3.46 (1H, m, H-5), 3.54-3.64 (1H, m, H-5'), 4.04-4.09 (1H, m, H-3), 4.12 (2H, t, *J* 6.7 Hz, OC<u>H</u>$_2$), 4.16-4.22 (1H, m, H-2), 4.38 (1H, t, *J* 4.0 Hz, H-4), 4.43-4.48 (2H, m, Ph-C<u>H</u>$_2$), 4.54 (4H, ABq, *J* 12.0 Hz, Ph-C<u>H</u>$_2$*)*, 5.44 (1H, d, $J_{NH,1}$ 12.0 Hz, H-1), 5.73 (1H, d, $J_{1,NH}$ 10.6 Hz, N<u>H</u>), 7.22-7.37 (15H, m, Ar-H); β anomer: 0.90 (3H, t, *J* 6.7 Hz, C<u>H</u>$_3$), 1.21-1.43 (14H, m, C<u>H</u>$_2$), 1.64-1.74 (2H, m, OCH$_2$C<u>H</u>$_2$), 3.49-3.54 (2H, m, H-5, H-5'), 4.04-4.09 (1H, m, H-3), 4.12 (2H, t, *J* 6.7 Hz, OC<u>H</u>$_2$), 4.16-4.22 (2H, m, H-2, H-4), 4.54 (6H, m, Ph-C<u>H</u>$_2$), 5.04 (1H, dd, $J_{1,2}$ 3.9 Hz, $J_{1,NH}$ 10.4 Hz, H-1), 5.79 (1H, d, $J_{1,NH}$ 10.2 Hz, N<u>H</u>), 7.22-7.37 (15H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.1 (q, CH_3), 22.7, 25.5, 28.7, 29.1, 29.3, 29.4, 29.5, 31.8 (8 x t, 8 x CH_2), 69.7, 69.9 (2 x t, C-5α, C-5β), 71.2 (t, CH_2O), 71.4, 71.7, 71.9, 72.3, 73.3, 73.6 (6 x t, Ph-<u>C</u>H$_2$), 80.8, 80.8 (2 x d, C-2β, C-4β), 82.0 (d, C-3β), 82.1 (d, C-2α), 83.3 (d, C-4α), 84.1 (d, C-1β), 84.7 (d, C-3α), 88.1 (d, C-1α), 127.6, 127.8, 127.9, 128.5, 128.6 (5 x d, 5 x Ar-C), 136.7, 137.4, 137.5 (3 x s, 3 x Ar-<u>C</u>); HRMS (ESI) calculated for $C_{36}H_{49}NNaO_7S$ 662.3127. Found 662.3121 (MNa^+).

1,1,1-Trifluoro-*N*-(β-D-arabinofuranosyl)methanesulfonamide 2.26a



10 % Activated Pd/C (10 mg) was added to a solution of 1,1,1-trifluoro-*N*-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)methanesulfonamide **2.25a** (40 mg, 0.1 mmol) in methanol. The flask was evacuated and purged with nitrogen five times, before being placed under an atmosphere of hydrogen. The solution was stirred for 16 hours at

room temperature. After this time, t.l.c. (ethyl acetate) indicated the formation of a single product (R_f 0.0), and the complete consumption of starting material (R_f 0.9). The reaction mixture was filtered through Celite® (eluting with methanol, 20 mL), and concentrated *in vacuo* to give a residue which was purified by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50 -80 % B; column oven 15 °C; detection: CAD) to afford de-protected triflurosulfonamide **2.26a** (13 mg, 65 %) as waxy yellow solid. $[\alpha]_D^{20}$ +36.4 (*c*, 0.5 in CH_3OH); υ_{max} (neat) 3288 (br s, OH), 1316 (s, S=O), 1150 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3OD) 3.64 (1H, dd, $J_{4,5}$ 5.8 Hz, $J_{5,5'}$ 11.7 Hz, H-5), 3.74 (1H, dd, $J_{4,5'}$ 4.3 Hz, $J_{5.5'}$ 12.5 Hz, H-5'), 3.84-3.86 (1H, dd, $J_{3,4}$ 5.7 Hz, $J_{2,3}$ 3.3 Hz, H-3), 3.97-4.00 (1H, aq, *J* 5.1 Hz, H-4), 4.02 (1H, m, H-2), 5.17 (1H, s, H-1); δ_C (100 MHz, CD_3OD) 61.7 (t, C-5), 77.4 (d, C-3), 81.9 (d, C-2), 84.8 (d, C-4), 103.9 (d, C-1), 118.3 (q, $J_{C,F}$ 324.2 HZ, CF_3); δ_F (376.6 MHz, CD_3OD) -81.59; HRMS (ESI) calculated for $C_6H_{10}F_3NNaO_6S$ 304.0079. Found 304.0090 (MNa^+).

Experimental procedure for attempted equilibration of 2.26a.

The purified β-furanose trifluoromethanesulfonamide **2.26a** (1 mg, 0.003 mmol) was dissolved in a mixture of H_2O and MeOH (4:1), and equilibration was analysed by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven: 15 °C; detection: CAD) over a 48 hour time period. No mutarotation or equilibration to the pyranose form was observed. The results are shown in **Figure 5.1.**

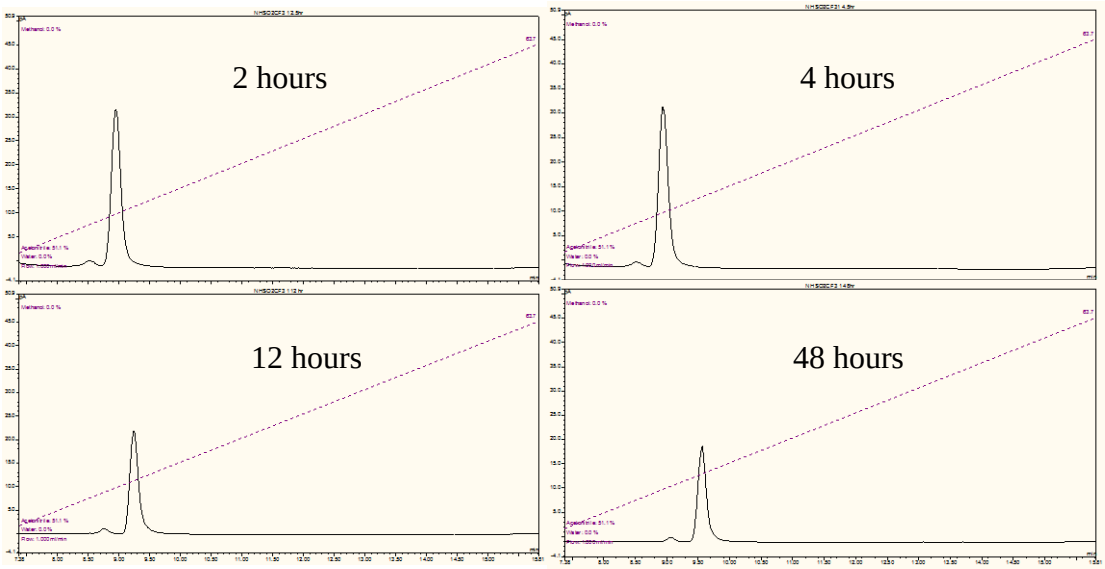
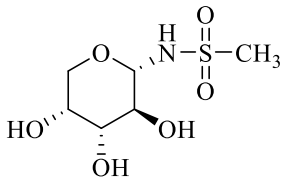


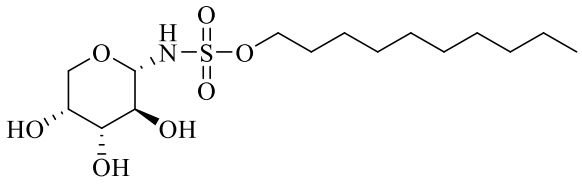
Figure 5.1 RP-HPLC traces and time-dependence of equilibration of 1,1,1-trifluoro-*N*-(β-D-arabinofuranosyl)methanesulfonamide **2.26a** in methanol/water.

***N* -(α-D-Arabinopyranosyl)methanesulfonamide 2.26b**



10 % Activated Pd/C (15 mg) was added to a solution of *N*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)methanesulfonamide **2.25b** (60 mg, 0.1 mmol) in methanol. The flask was evacuated and purged with nitrogen five times, before being placed under an atmosphere of hydrogen. The solution was then stirred for 16 hours at room temperature. After this time, t.l.c. (ethyl acetate) indicated the formation of a single product (R_f 0.0), and the complete consumption of starting material (R_f 0.9). The reaction mixture was filtered through Celite® (eluting with methanol, 20 mL), and concentrated *in vacuo* to give a residue which was purified by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a isocratic flow of 20 % B; column oven: 15 °C; detection: CAD) to afford de-protected methanesulfonamide **2.26b** (9 mg, 33 %) as white solid. α-anomer: m.p. 178-180 °C (MeOH/diethyl ether); $[\alpha]_D^{20}$ -16 (*c*, 0.5 in CH_3OH); υ_{max} (neat) 3280 (br s, OH), 1328 (s, S=O), 1159 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 3.01 (3H, s, C<u>H</u>$_3$), 3.48 (1H, at, $J_{1,2}$ 7.9 Hz, H-2), 3.53-3.59 (2H, m, H-3, H-5), 3.79-3.84 (1H, m, H-4, H-5'), 4.36 (1H, d, $J_{1,2}$ 7.6 Hz, H-1); δ_C (100 MHz, CD_3OD) 42.0 (q, CH_3), 66.9 (d, C-5), 68.3 (d, C-4), 69.8 (d, C-2), 73.4 (d, C-3), 85.2 (d, C-1); HRMS (ESI) calculated for $C_6H_{13}NNaO_6S$ 250.0361. Found 250.0365 (MNa^+).

Decyl-*N*-(α-D-arabinopyranosyl)sulfamate 2.26c



10 % Activated Pd/C (20 mg) was added to a solution of decyl-*N*-(2,3,5-tri-*O*-benzyl-α,β-D-arabinofuranosyl)sulfamate **2.25c** (80 mg, 0.1 mmol) in methanol. The flask was evacuated and purged with nitrogen five times, before being placed under an atmosphere of hydrogen. The solution was then stirred for 16 hours at room temperature. After this time, t.l.c. (ethyl acetate) indicated the formation of a single product (R_f 0.0), and the complete consumption of starting material (R_f 0.9). The reaction mixture was filtered through Celite® (eluting with methanol, 20 mL), and concentrated *in vacuo* to give a residue which was purified by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 50-85 % B; column oven 15 °C; detection: CAD) to afford de-protected sulfamate **2.26c** (21 mg, 45 %) as white solid. $[\alpha]_D^{20}$ -5.4 (*c*, 0.5 in CH_3OH); m.p. 138-140 °C (MeOH/diethylether); υ_{max} (neat) 3334 (br s, OH), 1344 (s, S=O), 1178 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) 0.91 (3H, t, *J* 6.5 Hz, C<u>H</u>$_3$), 1.27-1.39 (14H, m, C<u>H</u>$_2$), 1.66-1.74 (2H, m, OCH$_2$C<u>H</u>$_2$), 3.47 (1H, at, *J* 7.8 Hz, H-2), 3.52-3.58 (2H, m, H-3, H-5), 3.77-3.80 (1H, m, H-4), 3.83 (1H, d, $J_{4,5'}$ 2.7 Hz, H-5'), 4.15 (2H, t, *J* 6.5 Hz, C<u>H</u>$_2$O), 4.31 (1H, d, $J_{1,2}$ 7.8 Hz, H-1); δ_C (100 MHz, CD_3OD) 13.0 (q, CH_3), 22.3, 25.2, 28.4, 29.2, 31.8 (5 x t, 8 x CH_2), 67.1 (t, C-5), 68.4 (d, C-4), 69.9 (d, C-2), 70.3 (t, CH_2O), 73.5 (d, C-3), 85.3 (d, C-1); HRMS (ESI) calculated for $C_{15}H_{31}NNaO_7S$ 392.1719. Found 392.1707 (MNa^+).

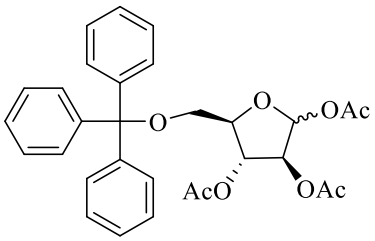
General Procedure A:

Arabinofuranosyl acetates **2.29, 2.30, 2.32** and **2.34** (1 equiv.), and the sulfamide (1 equiv.) were stirred at room temperature in dry DCM (15 mL) under nitrogen. $BF_3.OEt_2$ (2 equiv.) was added dropwise, and the mixture was then stirred for 16 h. The reaction was then neutralized by the dropwise addition of excess triethylamine (~0.3 mL). The reaction mixture was then filtered through Celite®, eluting with ethyl acetate, and concentrated *in vacuo* to give a residue which was purified by flash chromatography.

General Procedure B:

Glycosyl sulfamides **2.35a-c** and **2.39a-c** was dissolved in dry methanol (~5 mL). Sodium metal (0.1 equiv.) was added, and the mixture was then stirred for 1 h. Dowex® 50WX8 (H^+) was added the pH was neutral. The reaction mixture was then filtered, and concentrated *in vacuo* to give a residue which was purified by flash chromatography.

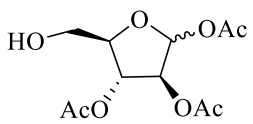
1,2,3-Tri-*O*-acetyl-5-*O*-trityl-D-arabinofuranose 2.27[15]



D-Arabinose (2 g, 13 mmol, 1 equiv.) was dissolved by heating in pyridine (35 mL), and solution allowed to cool to room temperature before trityl chloride (3.7 g, 13

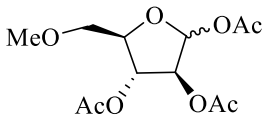
mmol, 1 equiv.) was added portion-wise. The reaction mixture was then stirred for 48 h under nitrogen. The reaction was quenched by the addition of with MeOH (10 mL), and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (30 mL) and the organic layer was washed with water (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue that was then purified by flash chromatography (Petrol: EtOAc 1:1, to Petrol: EtOAc 1:8), afforded 5-*O*-trityl-D-arabinofuranose (2.1 g, 41 %). The product (1.8 g, 4.5 mmol) was then dissolved pyridine (20 mL) and acetic anhydride (3.5 mL) was added dropwise at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature, and then stirred for 16 h. The solvent was removed *in vacuo* and the residue was dissolved in DCM (20 mL). The solution was washed with saturated aqueous $NaHCO_3$ (3 x 20 mL), and brine (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue that was then purified by flash chromatography (Petrol: EtOAc 1:1, R_f 0.5), to afford 1,2,3-tri-*O*-acetyl-5-*O*-trityl-D-arabinofuranose **2.27** (2.0 g, 84 % α:β, 2:1) as a colourless oil. δ_H (400 MHz, $CDCl_3$) α anomer: 2.07, 2.08, 2.11 (9H, 3 x s, 3 x OAc), 3.29-3.35 (2H, m, H-5, H-5'), 4.32 (1H, aq, *J* 4.7 Hz, H-4), 5.25 (1H, d, $J_{2,3}$ 1.6 Hz, H-2), 5.27 (1H, d, $J_{3,4}$ 4.7 Hz, H-3), 6.21 (1H, s, H-1); β anomer: 2.03, 2.05, 2.07 (9H, 3 x s, 3 x OAc), 3.29-3.35 (2H, m, H-5, H-5'), 4.17 (1H, aq, *J* 5.5 Hz, H-4), 5.33 (1H, dd, $J_{1,2}$ 4.8 Hz, $J_{2,3}$ 7.2 Hz, H-2), 5.56 (1H, at, *J* 6.7 Hz, H-3), 6.38 (1H, d, $J_{1,2}$ 4.8 Hz, H-1).

1,2,3-Tri-*O*-acetyl-D-arabinofuranose 2.28[15]



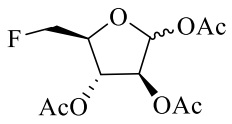
1,2,3-Tri-*O*-acetyl-5-*O*-trityl-D-arabinofuranose **2.27** (2 g, 3.8 mmol) was dissolved in a mixture of water and acetic acid (20 mL, 1:4, v/v), and then stirred at 100 °C for 25 min. After this time, t.l.c. (petrol: EtOAc 1:1) indicated the formation of a single product (R_f 0.2), and the complete consumption of starting material (R_f 0.5). The reaction was cooled in an ice-bath, and the crystallized trityl alcohol was filtered off. Brine (40 mL) was added to the filtrate, and the mixture was extracted with DCM (3 x 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue that was then purified by flash chromatography (petrol: EtOAc 5:1 to 2:3) to afford alcohol **2.28** (790 mg, 74 %, α:β, 2:1) as a colourless oil. δ_H (400 MHz, $CDCl_3$) α anomer: 2.07, 2.10, 2.11 (9H, 3 x s, 3 x OAc), 3.72-3.91 (2H, m, H-5, H-5'), 4.23 (1H, aq, *J* 4.0 Hz, H-4), 5.12 (1H, dd, $J_{2,3}$ 1.2 Hz, $J_{3,4}$ 5.1 Hz, H-3), 5.25 (1H, d, $J_{2,3}$ 1.2 Hz, H-2), 6.17 (1H, s, H-1); β anomer: 2.12, 2.13, 2.13 (9H, 3 x s, 3 x OAc), 3.72-3.91 (2H, m, H-5, H-5'), 4.08 (1H, aq, *J* 5.2 Hz, H-4), 5.38-5.40 (2H, m, H-2, H-3), 6.38 (1H, d, $J_{1,2}$ 3.2 Hz, H-1).

1,2,3-Tri-*O*-acetyl-5-*O*-methyl-D-arabinofuranose 2.29[15]



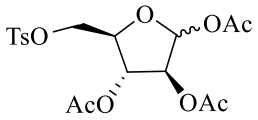
1,2,3-Tri-*O*-acetyl-D-arabinofuranose **2.28** (300 mg, 1.0 mmol, 1 equiv.), 2,6-di-*tert*butyl-4-methylpyridine (498 mg, 2.6 mmol, 2.4 equiv.) and $Hg(CN)_2$ (2.7 mg, 0.001 mmol, 0.01 equiv.) were stirred in DCM (25 mL) at room temperature under nitrogen. Methyl triflate (0.26 mL, 2.3 mmol, 2.2 equiv.) was added, and the mixture stirred for 5 min. The reaction mixture was then heated to 40 °C for 24 h. After this time, t.l.c. (petrol: EtOAc 2:1) indicated the formation of a single product (R_f 0.2), and the complete consumption of starting material (R_f 0.0). The reaction mixture was washed with 1 M aqueous HCl (2 × 50 mL) and brine (50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue that was then purified by flash chromatography (petrol: EtOAc 12:1 to 3:1) to afford methyl ether **2.29** (197 mg, 63 %, α:β, 2:1) as a colourless oil; δ_H (400 MHz, $CDCl_3$) α anomer: 2.10, 2.11, 2.12 (9H, 3 x s, 3 x OAc), 3.39 (3H, s, OCH_3), 3.54-3.67 (2H, m, H-5, H-5'), 4.28-4.31 (1H, m, H-4), 5.11 (1H, dd, $J_{2,3}$ 1.4 Hz, $J_{3,4}$ 5.3 Hz, H-3), 5.19 (1H, d, $J_{2,3}$ 1.6 Hz, H-2), 6.20 (1H, s, H-1); β anomer: 2.07, 2.09, 2.09 (9H, 3 x s, 3 x OAc), 3.41 (3H, s, OCH_3), 3.54-3.67 (2H, m, H-5, H-5'), 4.12-4.16 (1H, m, H-4), 5.33-5.36 (1H, m, H-2), 5.38-5.42 (1H, m, H-3), 6.36 (1H, d, $J_{1,2}$ 4.3 Hz, H-1).

1,2,3-Tri-*O*-acetyl-5-fluoro-5-deoxy-D-arabinofuranose 2.30[15]



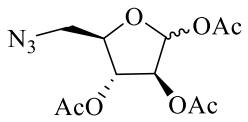
1,2,3-Tri-*O*-acetyl-D-arabinofuranose **2.28** (340 mg, 1.2 mmol, 1 equiv.), was stirred in dry diglyme (5 mL). The mixture was stirred at room temperature for 5 min under nitrogen before it was cooled to −40 °C. (Diethylamino)sulfur trifluoride (DAST) (0.81 mL, 6.1 mmol, 5 equiv.) was added, and the mixture was then stirred for 30 min. The reaction was then allowed to warm to room temperature and stirred for 16 hours. After this time, t.l.c. (petrol: EtOAc 2:1) indicated the formation of a single product (R_f 0.6), and the complete consumption of starting material (R_f 0.0). The reaction was carefully quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). The mixture was extracted with diethyl ether (3 × 25 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was purified by flash chromatography (petrol: EtOAc1:1) to afford fluoride **2.30** (213 mg, 62%, α:β, 2:1) as a colourless oil. δ_H (400 MHz, $CDCl_3$) α anomer: 2.11, 2.12, 2.14 (9H, 3 x s, 3 x OAc), 4.28-4.37 (1H, m, H-4), 4.48-4.72 (2H, m, H-5, H-5'), 5.11 (1H, d, $J_{3,4}$ 4.7 Hz, H-3), 5.23 (1H, s, H-2), 6.22 (1H, s, H-1); β anomer: 2.07, 2.09, 2.09, (9H, 3 x s, 3 x OAc), 4.13-4.22 (1H, m, H-4), 4.48-4.72 (4H, m, H-5, H-5'), 5.36 (1H, dd, $J_{1,2}$ 4.7 Hz, $J_{3,4}$ 7.0 Hz, H-2), 5.41-5.46 (1H, m, H-3), 6.37 (1H, d, $J_{1,2}$ 4.7 Hz, H-1).

1,2,3-Tri-*O*-acetyl-5-*O*-tosyl-D-arabinofuranose 2.31[15]



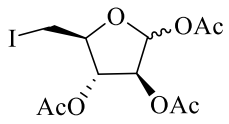
1,2,3-Tri-*O*-acetyl-D-arabinofuranose **2.28** (210 mg, 0.8 mmol, 1 equiv.) was dissolved in a mixture of dry DCM (20 mL) and pyridine (5 mL). Tosyl chloride (217 mg, 1.1 mmol 1.5 equiv.) was then added slowly. The reaction mixture was stirred at room temperature for 48 h under nitrogen. After this time, t.l.c. (petrol: EtOAc 1:1) indicated the formation of a single product (R_f 0.4), and the complete consumption of starting material (R_f 0.2). The reaction mixture was washed with water and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were washed with 1 M aqueous HCl (20 mL), saturated aqueous $NaHCO_3$, and brine (30 mL), and then dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The residue was purified by flash chromatography (petrol: EtOAc 1:1) to afford tosylate **2.31** (190 mg, 58 %, α:β, 2:1), as a colourless oil. δ_H (400 MHz, $CDCl_3$) α anomer: 2.09, 2.10, 2.11 (9H, 3 x s, 3 x OAc), 2.45 (3H, s, CH_3), 4.15-4.33 (3H, m, H-4, H-5, H-5'), 4.98-5.01 (1H, m, H-3), 5.16 (1H, d, $J_{2,3}$ 0.5 Hz, H-2), 6.12 (1H, s, H-1), 7.35 (2H, d, *J* 8.2 Hz, Ar-H), 7.80 (2H, d, *J* 7.4 Hz, Ar-H); β anomer: 2.05, 2.07, 2.08 (9H, 3 x s, 3 x OAc), 2.45 (3H, s, CH_3), 4.15-4.33 (3H, m, H-4, H-5, H-5'), 5.29-5.32 (2H, m, H-2, H-3), 6.33 (1H, d, $J_{1,2}$ 3.8 Hz, H-1), 7.35 (2H, d, *J* 8.2 Hz, Ar-H), 7.80 (2H, d, *J* 7.4 Hz, Ar-H).

1,2,3-Tri-*O*-acetyl-5-azido-5-deoxy-D-arabinofuranose 2.32[15]



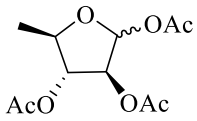
1,2,3-Tri-*O*-acetyl-5-*O*-tosyl-D-arabinofuranose **2.31** (230 mg, 0.5 mmol) and sodium azide (139 mg, 2.1 mmol, 4 equiv.) were heated to 80 °C in DMSO (15 mL). The reaction was stirred for 24 h under nitrogen. After this time, t.l.c. (petrol: EtOAc1:1) indicated the formation of a single product (R_f 0.6), and the complete consumption of starting material (R_f 0.4). The reaction was allowed to cool to room temperature and then diluted with DCM (40 mL), and washed with water (50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue that was then purified by flash chromatography (petrol:EtOAc 2 : 1) to afford azide **2.32** as a colourless oil (90 mg, 56 %, α:β, 2:1). δ_H (400 MHz, $CDCl_3$) α anomer: 2.12, 2.13, 2.14 (9H, 3 x s, 3 x OAc), 3.47-3.49 (1H, m, H-5), 3.68 (1H, dd, $J_{4,5}$ 3.1 Hz, $J_{5,5'}$ 13.3 Hz, H-5'), 4.30 (1H, aq, *J* 4.2 Hz, H-4), 5.05 (1H, d, $J_{3,4}$ 4.7 Hz, H-3), 5.22 (1H, s, H-2), 6.23 (1H, s, H-1); β anomer: 2.09, 2.10, 2.12 (9H, 3 x s, 3 x OAc), 3.43-3.46 (1H, m, H-5), 3.60 (1H, dd, $J_{4,5}$ 3.3 Hz, $J_{5,5'}$ 13.5 Hz, H-5'), 4.10-4.15 (1H, m, H-4), 5.36-5.39 (2H, m, H-2, H-3), 6.40 (1H, d, $J_{1,2}$ 4.0 Hz, H-1).

1,2,3-Tri-*O*-acetyl-5-iodo-5-deoxy-D-arabinofuranose 2.33[15]



1,2,3-Tri-*O*-acetyl-D-arabinofuranose **2.28** (210 mg, 0.8 mmol, 1 equiv.), triphenylphosphine (289 mg, 1.1 mmol, 1.45 equiv.), imidazole (155 mg, 2.3 mmol, 3 equiv.) and iodine (289 mg, 1.1 mmol, 1.5 equiv.) were stirred in dry toluene (20 mL) before heating the mixture to 100 °C for 2.5 h. After this time, t.l.c. (petrol: EtOAc 1:1) indicated the formation of a single product (R_f 0.7), and the complete consumption of starting material (R_f 0.2). The reaction was allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in DCM (20 mL). The solution was washed with 10 % aqueous $Na_2S_2O_3$ (30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue that was then purified by flash chromatography (petrol: EtOAc 2 : 1) to afford iodide **2.33** as a colourless oil (260 mg, 89 %, α:β, 1.5:1). δ_H (500 MHz, $CDCl_3$) α anomer: 2.11, 2.12, 2.13 (9H, 3 x s, 3 x OAc), 3.35-3.46 (2H, m, H-5, H-5'), 4.16-4.24 (1H, s, H-4), 4.99 (1H, d, $J_{3,4}$ 4.6 Hz, H-3), 5.20 (1H, s, H-2), 6.20 (1H, s, H-1), β anomer: 2.07, 2.07, 2.10 (9H, 3 x s, 3 x OAc), 3.35-3.46 (2H, m, H-5, H-5'), 4.16-4.24 (1H, s, H-4), 5.32-5.37 (2H, m, H-2, H-3), 6.39 (1H, d, $J_{1,2}$ 3.9 Hz, H-1).

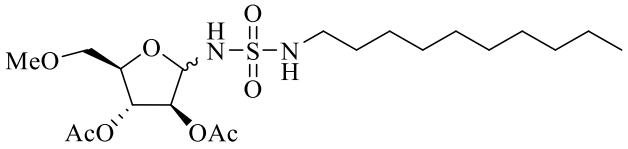
1,2,3-Tri-*O*-acetyl-5-deoxy-D-arabinofuranose 2.34[15]



Iodide **2.37** (380 mg, 1.0 mmol), triethylamine (0.11 mL, 0.8 mmol) and 10% Pd/C (78 mg, 25% w/w) were stirred in ethanol (5 mL), and the flask was evacuated and purged with nitrogen three times, before it was placed under an atmosphere of hydrogen. The solution was then stirred for 16 h at room temperature. After this time, t.l.c. (petrol: EtOAc 1:1) indicated the formation of a single product (R_f 0.9), and the complete consumption of starting material (R_f 0.7). The reaction mixture was filtered through Celite® (eluting with methanol, 20 mL), and concentrated *in vacuo* to give a residue which was purified by flash column chromatography (petrol: EtOAc 2:1) to afford 1,2,3-tri-*O*-acetyl-5-deoxy-D-arabinofuranose **2.34** (190 mg, 74 %, α:β, 1:1) as a colourless oil. δ_H (500 MHz, $CDCl_3$) α anomer: 1.41 (3H, d, $J_{4,5}$ 6.3 Hz, CH_3), 2.11, 2.11, 2.11 (9H, 3 x s, 3 x OAc), 4.26 (1H, quint, J 6.1 Hz, H-4), 4.84 (1H, dd, $J_{2,3}$ 1.2 Hz, $J_{3,4}$ 5.5 Hz, H-3), 5.17-5.21 (1H, m, H-2), 6.13 (1H, s, H-1); β anomer: 1.45 (3H, d, $J_{4,5}$ 6.7 Hz, CH_3), 2.08, 2.09, 2.10 (9H, 3 x s, 3 x OAc), 4.11 (1H, quint, J 6.2 Hz, H-4), 5.17-5.21 (1H, m, H-3), 5.31 (1H, dd, $J_{1,2}$ 4.7 Hz, $J_{2,3}$ 6.7 Hz, H-2), 6.33 (1H, d, $J_{1,2}$ 4.3 Hz, H-1).

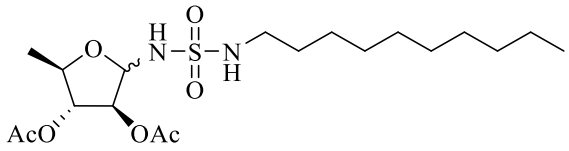
_N_-(Decyl)-_N_'-(2,3-di-_O_-acetyl-5-_O_-methyl-α,β-D-arabinofuranosyl)sulfamide

2.35a



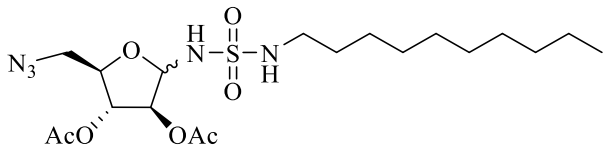
General Procedure A, using 1,2,3-tri-_O_-acetyl-5-_O_-methyl-D-arabinofuranose **2.29** (100 mg, 0.3 mmol) and _N_-(decyl)sulfamide[98] (81 mg, 0.3 mmol), and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.2), afforded glycosylsulfamide **2.35a** (120 mg, 75 %, α:β, 1:1) as a colourless oil; υ_{max} (neat) 3256 (N-H), 1756 (s, C=O), 1362 (s, S=O), 1167 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.87 (3H, t, _J_ 6.7 Hz, C<u>H</u>$_3$), 1.21-1.36 (14H, m, 7 x C<u>H</u>$_2$), 1.50-1.58 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.10, 2.11 (6H, 2 x s, 2 x OAc), 2.99-3.08 (2H, m, C<u>H</u>$_2$NH), 3.40 (3H, s, OC<u>H</u>$_3$), 3.55-3.59 (2H, m, H-5, H-5'), 4.21 (1H, aq, _J_ 4.3 Hz, H-4), 5.09-5.15 (2H, m, H-2, H-3), 5.30 (1H, d, $J_{NH,1}$ 10.1 Hz, H-1), 5.54 (1H, d, $J_{NH,1}$ 11.0 Hz N<u>H</u>); β anomer: 0.87 (3H, t, _J_ 6.7 Hz, C<u>H</u>$_3$), 1.21-1.36 (14H, m, C<u>H</u>$_2$), 1.50-1.58 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.09, 2.12 (6H, 2 x s, 2 x OAc), 2.99-3.08 (2H, m, C<u>H</u>$_2$NH), 3.46 (3H, s, OC<u>H</u>$_3$), 3.55-3.59 (1H, m, H-5), 3.64 (1H, dd, $J_{5,5'}$ 10.6 Hz, $J_{4,5'}$ 3.1Hz, H-5'), 3.93-3.97 (1H, m, H-4), 5.20-5.27 (2H, m, H-2, H-3), 5.45 (1H, dd, $J_{NH,1}$ 10.8 Hz, $J_{1,2}$ 5.3 Hz, H-1), 5.78 (1H, d, $J_{NH,1}$ 10.6 Hz N<u>H</u>); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, CH_3), 20.7, 20.7, 20.7, 20.8 (4 x q, 2 x OAc-α, 2 x OAc-β), 22.6, 26.7, 29.2, 29.3, 29.5, 29.5, 29.5, 31.9 (8 x t, 8 x CH_2), 43.2, 43.5 (2 x t, NHC<u>H</u>$_2$α, NHC<u>H</u>$_2$β), 59.4 (q, OC<u>H</u>$_3$), 72.1, 72.1 (t, C-5α, C-5β), 75.8 (d, C-2β), 75.8 (d, C-3β), 76.8 (d, C-3α), 79.9 (d, C-2α), 80.9 (d, C-4β), 82.1 (d, C-4α), 83.1 (d, C-1β), 88.1 (d, C-1α), 169.5, 169.7, 169.8, 170.3 (4 x s, 2 x OAc-α, 2 x OAc-β); HRMS (ESI) calculated for $C_{20}H_{39}N_2O_8S$: 467.2422. Found 467.2432 (MH^+).

_N_-(Decyl)-_N_'-(2,3-di-_O_-acetyl-5-deoxy-α,β-D-arabinofuranosyl)sulfamide 2.35b



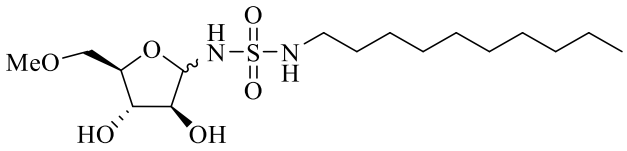
General Procedure A, using 1,2,3-tri-*O*-acetyl-5-deoxy-D-arabinofuranose **2.34** (190 mg, 0.7 mmol) and N-(decyl)sulfamide[98] (172 mg, 0.7 mmol), and purification by flash chromatography (petrol: EtOAc, 1:1, R_f 0.6), afforded glycosylsulfamide **2.35b** (180 mg, 57 %, α:β, 1:1) as a pale yellow waxy solid; υ_{max} (neat) 3294 (N-H), 1743 (s, C=O), 1372 (s, S=O), 1162 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.86 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$), 1.24-1.40 (17H, m, 7 x C$\underline{H}_2$, CH_3), 1.50-1.57 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.11, 2.15 (6H, 2 x s, 2 x OAc), 2.99-3.08 (2H, m, C$\underline{H}_2$NH), 4.16-4.24 (1H, m, H-4), 4.81-4.85 (1H, m, H-3), 5.08 (1H, s, H-2), 5.26 (1H, d, $J_{NH,1}$ 8.6 Hz, H-1), 5.59 (1H, d, $J_{NH,1}$ 9.0Hz, N$\underline{H}$); β anomer: 0.86 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$), 1.24-1.40 (17H, m, C$\underline{H}_2$, CH_3), 1.50-1.57 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.08, 2.10 (6H, 2 x s, 2 x OAc), 2.99-3.08 (2H, m, C$\underline{H}_2$NH), 3.81-3.88 (1H, m, H-4), 4.71-4.74 (1H, m, H-3), 5.15-5.19 (1H, m, H-2), 5.33 (1H, dd, $J_{NH,1}$ 10.8 Hz, $J_{1,2}$ 4.1 Hz, H-1), 5.51 (1H, d, $J_{NH,1}$ 11.0 Hz N$\underline{H}$); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, CH_3), 18.9, 19.2 (2 x q, C-5α, C-5β), 20.7, 20.7, 20.8, 20.8 (4 x q, 2 x OAc-α, 2 x OAc-β), 22.6, 26.7, 29.2, 29.3, 29.3, 29.4, 29.5, 31.8 (8 x t, 8 x CH_2), 43.4, 43.4 (2 x t, NHC$\underline{H}_2$α, NHC$\underline{H}_2$β), 75.9 (d, C-2β), 77.8 (d, C-4β), 79.6 (d, C-4α), 80.3 (d, C-3β), 80.5 (d, C-2α), 80.6 (d, C-3α), 83.4 (d, C-1β), 88.0 (d, C-1α), 169.2, 169.7, 169.8, 169.8 (4 x s, 2 x OAc-α, 2 x OAc-β); HRMS (ESI) calculated for $C_{19}H_{37}N_2O_7S$: 437.2316. Found 437.2302 (MH^+).

***N*-(Decyl)-*N*'-(2,3-di-*O*-acetyl-5-azido-α,β-D-arabinofuranosyl)sulfamide 2.35c**



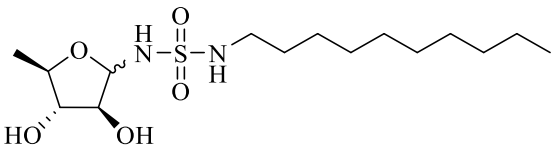
General Procedure A, using 1,2,3-tri-*O*-acetyl-5-azido-D-arabinofuranose **2.32** (90 mg, 0.3 mmol) and N-(decyl)sulfamide[98] (70 mg, 0.3 mmol), and purification by flash chromatography (petrol: EtOAc, 1:1, R_f 0.6), afforded glycosyl sulfamide **2.35c** (80 mg, 56 %, α:β, 1:1) as a pale yellow waxy solid; υ_{max} (neat) 3273 (N-H), 2098 (N_3), 1743 (s, C=O), 1370 (s, S=O), 1165 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.87 (3H, t, *J* 6.3 Hz, C<u>H</u>$_3$), 1.22-1.36 (14H, m, 7 x C<u>H</u>$_2$), 1.50-1.61 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.11, 2.19 (6H, 2 x s, 2 x OAc), 3.01-3.14 (2H, m, C<u>H</u>$_2$NH), 3.37-3.48 (1H, m, H-5), 3.53-3.63 (1H, m, H-5'), 4.21-4.26 (1H, m, H-4), 4.36-4.49 (1H, m, N<u>H</u>CH$_2$), 5.03-5.06 (1H, m, H-3), 5.16 (1H, d, *J* 1.6 Hz, H-2), 5.35 (1H, d, $J_{NH,1}$ 9.4 Hz, H-1), 5.49-5.56 (1H, m, N<u>H</u>); β anomer: 0.87 (3H, t, *J* 6.3 Hz, C<u>H</u>$_3$), 1.22-1.36 (14H, m, C<u>H</u>$_2$), 1.50-1.61 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.13, 2.13 (6H, 2 x s, 2 x OAc), 3.01-3.14 (2H, m, C<u>H</u>$_2$NH), 3.37-3.48 (1H, m, H-5), 3.53-3.63 (1H, m, H-5'), 3.91-3.95 (1H, m, H-4), 4.36-4.49 (1H, m, N<u>H</u>CH$_2$), 4.91-4.94 (1H, m, H-3), 5.18-5.21 (1H, m, H-2), 5.42 (1H, dd, $J_{NH,1}$ 10.6 Hz, $J_{1,2}$ 3.5 Hz, H-1), 5.49-5.56 (1H, m, N<u>H</u>); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, CH_3), 20.6, 20.7 (2 x q, 2 x OAc), 22.6, 26.7, 29.2, 29.3, 29.4, 29.5, 29.5, 31.9 (8 x t, 8 x CH_2), 43.5, 43.6 (2 x t, NHCH$_2$α, NHCH$_2$β), 51.7, 51.7 (t, C-5α, C-5β), 75.6 (d, C-2β), 76.5, 77.1 (2 x d, C-3α, C-3β), 79.7 (d, C-2α), 81.3 (d, C-4β), 82.6 (d, C-4α), 83.8 (d, C-1β), 88.1 (d, C-1α), 169.7, 169.9 (2 x s, 2 x OAc); HRMS (ESI) calculated for $C_{19}H_{35}N_5NaO_7S$: 500.2149. Found 500.2157 (MNa^+).

_N_-(Decyl)-_N_'-(5-_O_-methyl-α,β-D-arabinofuranosyl)sulfamide 2.36a



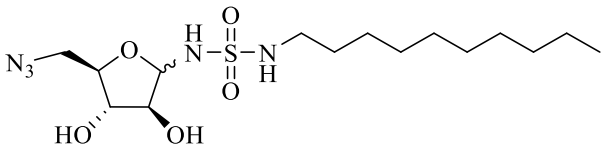
General Procedure B, using glycosyl sulfamide **2.35a** (60 mg, 0.1 mmol) and purification by flash chromatography (petrol: EtOAc, 1:1, R_f 0.1), afforded *N*-(decyl)-*N*'-(5-*O*-methyl-α,β-D-arabinofuranosyl)sulfamide **2.36a** (40 mg, 82 %, α:β, 1:1) as a white solid; m.p. 91-93 °C (MeOH/DCM); υ_{max} (neat) 3280 (N-H), 1347 (s, S=O), 1141 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) α anomer: 0.91 (3H, t, *J* 6.7 Hz, C<u>H</u>$_3$), 1.25-1.39 (14H, m, 7 x C<u>H</u>$_2$), 1.49-1.56 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.93-3.01 (2H, m, C<u>H</u>$_2$NH), 3.37 (3H, s, OC<u>H</u>$_3$), 3.47-3.54 (2H, m, H-5, H-5'), 3.87-3.92 (2H, m, H-2), 3.93-3.98 (1H, m, H-3), 4.04 (1H, aq, *J* 4.2 Hz, H-4), 4.92 (1H, d, $J_{NH,1}$ 10.4 Hz, H-1), 5.00-5.08 (1H, m, N<u>H</u>CH$_2$), 5.98 (1H, d, $J_{NH,1}$ 10.2 Hz, N<u>H</u>); β anomer: 0.91 (3H, t, *J* 6.7 Hz, C<u>H</u>$_3$), 1.25-1.39 (14H, m, 7 x C<u>H</u>$_2$), 1.49-1.56 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.93-3.01 (2H, m, C<u>H</u>$_2$NH), 3.38 (3H, s, OC<u>H</u>$_3$), 3.47-3.54 (2H, m, H-5, H-5'), 3.80 (1H, aq, *J* 3.5 Hz, H-4), 3.82-3.86 (2H, m, H-2), 3.93-3.98 (1H, m, H-3), 5.00-5.08 (1H, m, N<u>H</u>CH$_2$), 5.12 (1H, dd, $J_{NH,1}$ 10.2 Hz, $J_{1,2}$ 3.9 Hz, H-1), 5.76 (1H, d, $J_{NH,1}$ 10.6 Hz, N<u>H</u>); δ_C (100.5 MHz, CD_3CN) 13.4 (q, CH_3), 22.4, 26.5, 29.0, 29.0, 29.0, 29.1, 29.3, 31.6 (8 x t, 8 x CH_2), 43.0, 43.0 (2 x t, NHC<u>H</u>$_2$α, NHC<u>H</u>$_2$β), 58.5, 58.6 (2 x q, OC<u>H</u>$_3$α, OCH$_3$β), 72.5, 72.8 (t, C-5α, C-5β), 76.1 (d, C-2β), 76.6 (d, C-3β, C-3α), 79.9 (d, C-2α), 82.8 (d, C-4β), 84.4 (d, C-4α), 85.3 (d, C-1β), 89.9 (d, C-1α); HRMS (ESI) calculated for $C_{16}H_{35}N_2O_6S$: 383.2210. Found 383.2214 (MH^+).

***N*-(Decyl)-*N*'-(5-deoxy-α,β-D-arabinofuranosyl)sulfamide 2.36b**



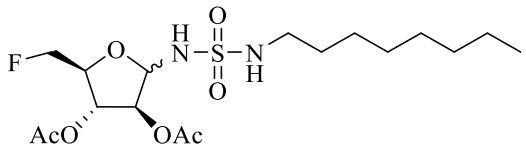
General Procedure B, using glycosyl sulfamide **2.35b** (80 mg, 0.2 mmol) and purification by flash chromatography (petrol: EtOAc, 1:1, R_f 0.1), afforded *N*-(decyl)-*N*'-(5-deoxy-α,β-D-arabinofuranosyl)sulfamide **2.36b** (52 mg, 81 %, α:β, 2:1) as a white solid; m.p. 100-102 °C (MeOH/DCM); υ_{max} (neat) 3287 (N-H), 1318 (s, S=O), 1149 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3OD) α anomer: 0.89 (3H, t, *J* 7.0 Hz, C<u>H</u>$_3$), 1.24-1.38 (17H, m, 7 x C<u>H</u>$_2$, CH_3), 1.49-1.57 (2H, m, NHCH_2C<u>H</u>$_2$), 2.94-3.02 (2H, m, C<u>H</u>$_2$NH), 3.66-3.70 (1H, m, H-3), 3.87-3.95 (2H, m, H-2, H-4), 4.91 (1H, d, $J_{1,2}$ 4.3 Hz, H-1); β anomer: 0.89 (3H, t, *J* 7.0 Hz, C<u>H</u>$_3$), 1.24-1.38 (17H, m, 7 x C<u>H</u>$_2$, CH_3), 1.49-1.57 (2H, m, NHCH_2C<u>H</u>$_2$), 2.94-3.02 (2H, m, C<u>H</u>$_2$NH), 3.57 (1H, at, *J* 6.7 Hz, H-3), 3.66-3.70 (1H, m, H-4), 3.87-3.95 (1H, m, H-2), 5.11 (1H, d, $J_{1,2}$ 4.7 Hz, H-1); δ_C (100.5 MHz, CD_3OD) 13.1 (q, CH_3), 17.6, 18.4 (2 x q, C-5α, C-5β), 22.3, 26.5, 29.0, 29.0, 29.1, 29.3, 31.7 (7 x t, 8 x CH_2), 42.6, 42.7 (2 x t, NHC<u>H</u>$_2$α, NHC<u>H</u>$_2$β), 76.5 (d, C-2β), 77.8 (d, C-4β), 78.5 (d, C-4α), 80.8 (d, C-3β), 81.0 (d, C-2α), 81.1 (d, C-3α), 84.4 (d, C-1β), 88.4 (d, C-1α); HRMS (ESI) calculated for $C_{15}H_{33}N_2O_5S$: 353.2105. Found 353.2112 (MH^+).

***N*-(Decyl)-*N*'-(5-azido-α,β-D-arabinofuranosyl)sulfamide 2.36c**



General Procedure B, using glycosyl sulfamide **2.35c** (80 mg, 0.2 mmol) and purification by flash chromatography (petrol: EtOAc, 1:1, R_f 0.1), afforded *N*-(decyl)-*N*'-(5-azido-α,β-D-arabinofuranosyl)sulfamide **2.36c** (42 mg, 62 %, α:β, 1:1) as a white solid; m.p. 99-101 °C (MeOH/DCM); υ_{max} (neat) 3293 (N-H), 2103 (N_3), 1340 (s, S=O), 1141 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) α anomer: 0.90 (3H, t, *J* 6.7 Hz, C<u>H</u>$_3$), 1.25-1.39 (14H, m, 7 x C<u>H</u>$_2$), 1.48-1.57 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.95-3.03 (2H, m, C<u>H</u>$_2$NH), 3.34-3.50 (2H, m, H-5, H-5'), 3.83-3.90 (1H, m, H-3), 3.92-3.98 (1H, m, H-2), 4.01 (1H, aq, *J* 3.9 Hz, H-4), 4.93 (1H, dd, $J_{NH,1}$ 10.2 Hz, $J_{1,2}$ 3.9 Hz, H-1), 4.99-5.12 (1H, m, N<u>H</u>CH$_2$), 6.07 (1H, d, $J_{NH,1}$ 10.2 Hz, N<u>H</u>); β anomer: 0.90 (3H, t, *J* 6.7 Hz, C<u>H</u>$_3$), 1.25-1.39 (14H, m, 7 x C<u>H</u>$_2$), 1.48-1.57 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.95-3.03 (2H, m, C<u>H</u>$_2$NH), 3.34-3.50 (2H, m, H-5, H-5'), 3.72-3.80 (1H, m, H-4), 3.83-3.90 (1H, m, H-3), 3.92-3.98 (1H, m, H-2), 5.17 (1H, dd, $J_{NH,1}$ 10.0 Hz, $J_{1,2}$ 4.1 Hz, H-1), 4.99-5.12 (1H, m, N<u>H</u>CH$_2$), 5.83 (1H, d, $J_{NH,1}$ 10.2 Hz, N<u>H</u>); δ_C (100.5 MHz, CD_3CN) 13.4 (q, CH_3), 22.4, 26.5, 29.0, 29.0, 29.1, 29.3, 31.7 (7 x t, 8 x CH_2), 43.0 (t, NHCH$_2$α, NHCH$_2$β), 52.2, 52.7 (t, C-5α, C-5β), 75.9 (d, C-2β), 76.3, 77.1 (2 x d, C-3α, C-3β), 79.9 (d, C-2α), 81.9 (d, C-4β), 82.1 (d, C-4α), 85.2 (d, C-1β), 89.1 (d, C-1α); HRMS (ESI) calculated for $C_{15}H_{31}N_5NaO_5S$: 416.1938. Found 416.1944 (MNa^+).

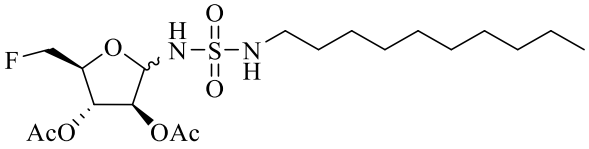
_N_-(Octyl)-_N_'-(2,3-di-_O_-acetyl-5-fluoro-α,β-D-arabinofuranosyl)sulfamide 2.37a



General Procedure A, using 1,2,3-tri-*O*-acetyl-5-fluoro-D-arabinofuranose **2.30** (60 mg, 0.2 mmol) and N-(octyl)sulfamide[98] (44 mg, 0.2 mmol), and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.35), afforded glycosyl sulfamide **2.37a** (48 mg, 53 %, α:β, 1:1) as a pale yellow waxy solid; υ_{max} (neat) 3279 (N-H), 1735 (s, C=O), 1369 (s, S=O), 1152 (s, S=O) cm^{-1};δ_H (400 MHz, $CDCl_3$) α anomer: 0.87 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$), 1.20-1.36 (10H, m, 5 x C$\underline{H}_2$), 1.51-1.58 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.14, 2.15 (6H, 2 x s, 2 x OAc), 3.01-3.13 (2H, m, C$\underline{H}_2$NH), 4.22-4.31 (1H, m, H-4), 4.51-4.56 (1H, m, H-5), 4.63-4.67 (1H, m, H-5'), 5.13 (1H, at, *J* 2.8 Hz, H-3), 5.16 (1H, at, *J* 2.3 Hz, H-2), 5.33 (1H, dd, $J_{NH,1}$ 9.6 Hz, $J_{1,2}$ 2.2 Hz, H-1), 5.37 (1H, d, $J_{NH,1}$ 11.0 Hz N$\underline{H}$); β anomer: 0.87 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$), 1.20-1.36 (10H, m, 5 x C$\underline{H}_2$), 1.51-1.58 (2H, m, NHCH$_2$C$\underline{H}_2$), 2.11, 2.13 (6H, 2 x s, 2 x OAc), 3.01-3.13 (2H, m, C$\underline{H}_2$NH), 3.90-4.01 (1H, m, H-4), 4.51-4.56 (1H, m, H-5), 4.63-4.67 (1H, m, H-5'), 5.05 (1H, dd, $J_{3,4}$ 3.5 Hz, $J_{2,3}$ 2.3 Hz, H-3), 5.22 (1H, dd, $J_{1,2}$ 4.1 Hz, $J_{2,3}$ 2.2 Hz, H-2), 5.48 (1H, dd, $J_{NH,1}$ 6.7 Hz $J_{1,2}$ 4.7 Hz, H-1), 5.45-5.46 (1H, m, N$\underline{H}$); δ_C (100.5 MHz, $CDCl_3$) 14.0 (q, CH_3), 20.6, 20.7, 20.7, 20.7 (4 x q, 2 x OAcα, 2 x OAcβ), 22.6, 26.7, 29.1, 29.4, 29.4, 31.7 (6 x t, 6 x CH_2), 43.4, 43.6 (2 x t, NHCH$_2$α, NHCH$_2$β), 75.2 (d, C-2β), 75.4 (d, $J_{c3\text{-}F}$ 6.1 Hz, C-3β), 75.9 (d, $J_{C3\text{-}F}$ 6.1 Hz, C-3α), 79.6 (d, C-2α), 81.5 (d, $J_{C4\text{-}F}$ 18.3 Hz, C-4β), 81.7 (d, $J_{C4\text{-}F}$ 19.8 Hz, C-4α), 82.1 (d, $J_{C5\text{-}F}$ 174.0 Hz, C-5β), 82.1 (d, $J_{C5\text{-}F}$ 174.0 Hz, C-5α), 83.7 (d, C-1β), 88.1 (d, C-1α), 169.3, 169.8, 169.9, 170.0 (4 x s, 2 x OAcα, 2 x OAcβ); δ_F (376.6 MHz, $CDCl_3$) -229.14 (td, $J_{F,H\ geminal}$ 40.1 Hz, $J_{F,H}$

$_{vicinal}$ 23.8 Hz, F-β), -229.34 (td, $J_{F,H\ geminal}$ 42.0 Hz, $J_{F,H\ vicinal}$ 23.8 Hz, F-α); HRMS (ESI) calculated for $C_{17}H_{32}FN_2O_7S$: 427.1909. Found 427.1900 (MH^+).

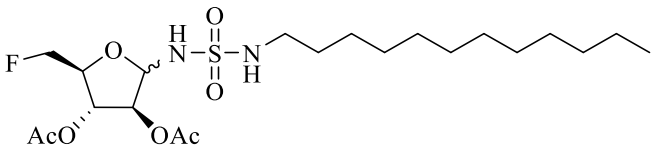
_N_-(Decyl)-_N_'-(2,3-di-_O_-acetyl-5-fluoro-α,β-D-arabinofuranosyl)sulfamide 2.37b



General Procedure A, using 1,2,3-tri-*O*-acetyl-5-fluoro-D-arabinofuranose **2.30** (75 mg, 0.3 mmol) and N-(decyl)sulfamide[98] (63 mg, 0.3 mmol), and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.4), afforded glycosylsulfamide **2.37b** (74 mg, 61 %, α:β, 1:1) as a pale yellow waxy solid; υ_{max} (neat) 3279 (N-H), 1735 (s, C=O), 1369 (s, S=O), 1152 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) α anomer: 0.78 (3H, t, *J* 6.3 Hz, C<u>H</u>$_3$), 1.13-1.30 (14H, m, 7 x C<u>H</u>$_2$), 1.41-1.52 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.00, 2.00 (6H, 2 x s, 2 x OAc), 2.87-2.96 (2H, m, C<u>H</u>$_2$NH), 4.20-4.32 (1H, m, H-4), 4.40-4.49 (1H, m, H-5), 4.51-4.61 (1H, m, H-5'), 5.04 (1H, at, *J* 3.9 Hz, H-3), 5.14 (1H, dd, $J_{NH,1}$ 9.0 Hz, $J_{1,2}$ 3.1 Hz, H-1), 5.21-5.24 (1H, m, H-2), 5.69-5.82 (1H, m, CH$_2$N<u>H</u>), 6.93 (1H, d, $J_{NH,1}$ 9.0 Hz, N<u>H</u>); β anomer: 0.78 (3H, t, *J* 6.3 Hz, C<u>H</u>$_3$), 1.13-1.30 (14H, m, 7 x C<u>H</u>$_2$), 1.41-1.52 (2H, m, NHCH$_2$C<u>H</u>$_2$), 1.95, 1.98 (6H, 2 x s, 2 x OAc), 2.87-2.96 (2H, m, C<u>H</u>$_2$NH), 3.88-3.99 (1H, m, H-4), 4.40-4.49 (1H, m, H-5), 4.51-4.61 (1H, m, H-5'), 4.97 (1H, at, *J* 3.1 Hz, H-3), 5.16-5.19 (1H, m, H-2), 5.33 (1H, dd, $J_{NH,1}$ 10.8 Hz $J_{1,2}$ 4.5 Hz, H-1), 5.69-5.82 (1H, m, CH$_2$N<u>H</u>), 6.72 (1H, d, $J_{NH,1}$ 11.0 Hz, N<u>H</u>); δ_C (100.5 MHz, CD_3CN) 13.3 (q, CH_3), 19.7, 19.7, 19.7 (3 x q, 2 x OAcα, 2 x OAcβ), 22.3, 26.5, 28.3, 28.5, 28.6, 28.8, 29.0, 31.6 (8 x t, 8 x CH_2), 42.8, 42.8 (2 x t, NHCH$_2$α, NHCH$_2$β), 74.6 (d, C-2β), 75.0 (d, $J_{c3\text{-}F}$ 7.6 Hz, C-3β), 75.2 (d,

$J_{C3\text{-}F}$ 6.9 Hz, C-3α), 79.2 (d, $J_{C4\text{-}F}$ 19.8 Hz, C-4β), 79.5 (d, C-2α), 80.1 (d, $J_{C4\text{-}F}$ 19.8 Hz, C-4α), 82.3 (d, $J_{C5\text{-}F}$ 171.7 Hz, C-5β), 82.3 (d, $J_{C5\text{-}F}$ 171.7 Hz, C-5α), 84.0 (d, C-1β), 87.6 (d, C-1α), 168.9, 169.1, 169.3, 169.6 (4 x s, 2 x OAcα, 2 x OAcβ); δ_F (376.6 MHz, $CDCl_3$) -229.18 (td, $J_{F,H\ geminal}$ 46.7 Hz, $J_{F,H\ vicinal}$ 23.8 Hz, F-β), -229.52 (td, $J_{F,H\ geminal}$ 47.7 Hz, $J_{F,H\ vicinal}$ 26.7 Hz, F-α); HRMS (ESI) calculated for $C_{19}H_{35}FN_2NaO_7S$: 477.2041. Found 477.2063 (MNa^+).

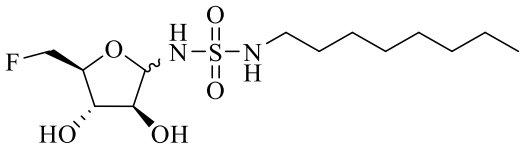
_N_-(Dodecyl)-_N_'-(2,3-di-_O_-acetyl-5-fluoro-α,β-D-arabinofuranosyl)sulfamide 2.37c



General Procedure A, using 1,2,3-tri-*O*-acetyl-5-fluoro-D-arabinofuranose **2.30** (70 mg, 0.3 mmol) and N-(dodecyl)sulfamide[98] (66 mg, 0.3 mmol), and purification by flash chromatography (petrol: EtOAc, 2:1, R_f 0.4), afforded glycosyl sulfamide **2.37c** (62 mg, 52 %, α:β, 1:1) as a pale yellow waxy solid; ; υ_{max} (neat) 3282 (N-H), 1755 (s, C=O), 1368 (s, S=O), 1151 (s, S=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) α anomer: 0.87 (3H, t, *J* 6.8 Hz, C<u>H</u>$_3$), 1.22-1.36 (18H, m, 9 x C<u>H</u>$_2$), 1.51-1.60 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.14, 2.15 (6H, 2 x s, 2 x OAc), 3.03-3.15 (2H, m, C<u>H</u>$_2$NH), 4.22-4.31 (1H, m, H-4), 4.48-4.56 (1H, m, H-5), 4.61-4.68 (1H, m, H-5'), 5.13 (1H, at, *J* 2.7 Hz, H-3), 5.14-5.17 (1H, m, H-2), 5.33 (1H, s, H-1); β anomer: 0.87 (3H, t, *J* 6.8 Hz, C<u>H</u>$_3$), 1.22-1.36 (18H, m, 9 x C<u>H</u>$_2$), 1.51-1.60 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.12 (6H, 1 x s, 2 x OAc), 3.03-3.15 (2H, m, C<u>H</u>$_2$NH), 3.90-4.01 (1H, m, H-4), 4.48-4.56 (1H, m, H-5), 4.61-4.68 (1H, m, H-5'), 5.06 (1H, dd, $J_{2,3}$ 2.3 Hz, $J_{3,4}$ 3.5 Hz, H-3), 5.22 (1H, dd, $J_{1,2}$ 4.3 Hz, $J_{2,3}$ 2.0 Hz, H-2), 5.28 (1H, d, $J_{NH,1}$ 11.0 Hz, N<u>H</u>), 5.48 (1H, dd, $J_{NH,1}$ 11.0 Hz, $J_{1,2}$ 4.7

Hz, H-1); δ_C (100.5 MHz, $CDCl_3$) 14.1 (q, CH_3), 20.7, 20.8, (2 x q, 2 x OAcα, 2 x OAcβ), 22.6, 26.6, 29.2, 29.3, 29.4, 29.5, 29.5, 29.6, 29.6, 31.9 (10 x t, 10 x CH_2), 43.5, 43.7 (2 x t, $NHCH_2$α, $NHCH_2$β), 75.3 (d, C-2β), 75.4 (d, $J_{C3\text{-}F}$ 6.9 Hz, C-3β), 76.0 (d, $J_{C3\text{-}F}$ 6.1 Hz, C-3α), 79.5 (d, C-2α), 80.6 (d, $J_{C4\text{-}F}$ 18.3 Hz, C-4β), 81.9 (d, $J_{C4\text{-}F}$ 19.8 Hz, C-4α), 82.1 (d, $J_{C5\text{-}F}$ 172.4 Hz, C-5β), 82.1 (d, $J_{C5\text{-}F}$ 175.5 Hz, C-5α), 83.7 (d, C-1β), 88.2 (d, C-1α), 169.2, 169.7, 169.8, 169.9 (4 x s, 2 x OAcα, 2 x OAcβ); δ_F (376.6 MHz, $CDCl_3$) -229.15 (td, $J_{F,H\ geminal}$ 47.7 Hz, $J_{F,H\ vicinal}$ 23.8 Hz, F-β), -229.6 (td, $J_{F,H\ geminal}$ 48.6 Hz, $J_{F,H\ vicinal}$ 27.7 Hz, F-α); HRMS (ESI) calculated for $C_{21}H_{40}FN_2O_7S$: 483.2535. Found 483.2523 (MH^+).

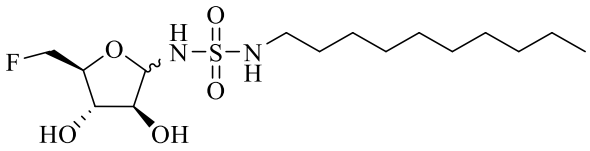
_N_-(Octyl)-_N_'-(5-fluoro-α,β-D-arabinofuranosyl)sulfamide 2.38a



General Procedure B, using glycosyl sulfamide **2.37a** (40 mg, 0.1 mmol) and purification by flash chromatography (petrol: EtOAc, 1:1, R_f 0.1), afforded *N*-(octyl)-*N*'-(5-fluoro-α,β-D-arabinofuranosyl)sulfamide **2.38a** (24 mg, 75 %, α:β, 1:1) as a white solid; m.p. 123-125 °C (MeOH/DCM); υ_{max} (neat) 3290 (N-H), 1347 (s, S=O), 1142 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) α anomer: 0.91 (3H, t, *J* 7.4 Hz, C<u>H</u>$_3$), 1.25-1.38 (10H, m, 5 x C<u>H</u>$_2$), 1.48-1.57 (2H, m, $NHCH_2C\underline{H}_2$), 2.93-3.02 (2H, m, C<u>H</u>$_2$NH), 3.91 (1H, at, *J* 4.3 Hz, H-3), 3.96 (1H, at, *J* 4.3 Hz, H-2), 4.03-4.11 (1H, m, H-4), 4.38-4.48 (1H, m, H-5), 4.51-4.60 (1H, m, H-5'), 4.91 (1H, d, $J_{1,2}$ 3.9 Hz, H-1), 5.07 (1H, br s, N<u>H</u>); β anomer: 0.91 (3H, t, *J* 7.4 Hz, C<u>H</u>$_3$), 1.25-1.38 (10H, m, 5 x C<u>H</u>$_2$), 1.48-1.57 (2H, m, $NHCH_2C\underline{H}_2$), 2.93-3.02 (2H, m, C<u>H</u>$_2$NH), 3.81-3.89 (1H, m,

H-4), 3.91 (1H, at, *J* 4.3 Hz, H-3), 4.00-4.02 (1H, m, H-2), 4.38-4.48 (1H, m, H-5), 4.51-4.60 (1H, m, H-5'), 5.19 (1H, d, $J_{1,2}$ 4.3 Hz, H-1), 5.07 (1H, br s, NH); δ_C (100.5 MHz, CD_3CN) 13.4 (q, CH_3), 22.4, 26.5, 28.9, 28.9, 29.0, 31.6 (6 x t, 6 x CH_2), 43.0 (t, $NHCH_2\alpha$, $NHCH_2\beta$), 74.7, 75.5 (2 x d, $J_{C3\text{-}F}$ 6.9 Hz, C-3β, C-3α), 75.7 (d, C-2β), 79.9 (d, C-2α), 81.5 (d, $J_{C4\text{-}F}$ 19.8 Hz, C-4β), 81.6 (d, $J_{C4\text{-}F}$ 19.1 Hz, C-4α), 83.0 (d, $J_{C5\text{-}F}$ 200.7 Hz, C-5β), 83.3 (d, $J_{C5\text{-}F}$ 137.3 Hz, C-5α), 85.0 (d, C-1β), 89.1 (d, C-1α); δ_F (376.6 MHz, $CDCl_3$) -226.26 (td, $J_{F,H\ geminal}$ 49.6 Hz, $J_{F,H\ vicinal}$ 19.1 Hz, F-β), -228.46 (td, $J_{F,H\ geminal}$ 48.6 Hz, $J_{F,H\ vicinal}$ 21.0 Hz, F-α); HRMS (ESI) calculated for $C_{13}H_{28}FN_2O_5S$: 343.1697. Found 343.1700 (MH^+).

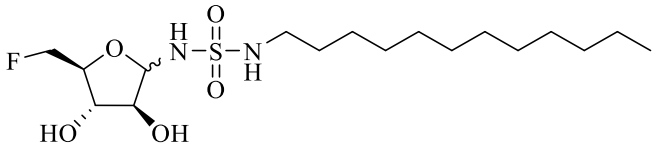
_N_-(Decyl)-_N_'-(5-fluoro-α,β-D-arabinofuranosyl)sulfamide 2.38b



General Procedure B, using glycosyl sulfamide **2.37b** (60 mg, 0.1 mmol) and purification by flash chromatography (petrol: EtOAc, 1:1, R_f 0.1), afforded *N*-(decyl)-*N*'-(5-fluoro-α,β-D-arabinofuranosyl)sulfamide **2.38b** (35 mg, 72 %, α:β, 3:1) as a white solid; m.p. 98-100 °C (MeOH/DCM); υ_{max} (neat) 3293 (N-H), 1329 (s, S=O), 1143 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3OD) α anomer: 0.89 (3H, t, *J* 6.8 Hz, CH_3), 1.24-1.40 (14H, m, 7 x CH_2), 1.49-1.56 (2H, m, $NHCH_2CH_2$), 2.94-3.04 (2H, m, CH_2NH), 3.93 (1H, at, *J* 2.7 Hz, H-3), 3.97 (1H, at, *J* 3.5 Hz, H-2), 3.99-4.06 (1H, m, H-4), 4.37-4.47 (1H, m, H-5), 4.49-4.58 (1H, m, H-5'), 4.93 (1H, d, $J_{1,2}$ 4.7 Hz, H-1); β anomer: 0.89 (3H, t, *J* 6.8 Hz, CH_3), 1.24-1.40 (14H, m, 7 x CH_2), 1.49-1.56 (2H, m, $NHCH_2CH_2$), 2.94-3.04 (2H, m, CH_2NH), 3.82-3.89 (1H, m, H-4), 3.91 (1H, at, *J*

4.3 Hz, H-3), 3.98-4.00 (1H, m, H-2), 4.37-4.47 (1H, m, H-5), 4.49-4.58 (1H, m, H-5'), 5.24 (1H, d, $J_{1,2}$ 4.3 Hz, H-1); δ_C (100.5 MHz, CD_3OD) 13.0 (q, CH_3), 22.3, 26.5, 29.0, 29.0, 29.1, 29.3, 31.7 (7 x t, 8 x CH_2), 42.6 (t, $NHCH_2\alpha$, $NHCH_2\beta$), 74.3, 75.6 (2 x d, $J_{C3\text{-}F}$ 6.9 Hz, C-3β, C-3α), 75.7 (d, C-2β), 80.1 (d, C-2α), 80.9 (d, $J_{C4\text{-}F}$ 19.1 Hz, C-4β), 81.7 (d, $J_{C4\text{-}F}$ 19.8 Hz, C-4α), 82.0 (d, $J_{C5\text{-}F}$ 170.9 Hz, C-5β), 82.7 (d, $J_{C5\text{-}F}$ 170.1 Hz, C-5α), 85.2 (d, C-1β), 88.6 (d, C-1α); δ_F (376.6 MHz, CD_3OD) -227.20 (td, $J_{F,H\ geminal}$ 47.7 Hz, $J_{F,H\ vicinal}$ 19.1 Hz, F-β), -230.70 (td, $J_{F,H\ geminal}$ 47.7 Hz, $J_{F,H\ vicinal}$ 23.8 Hz, F-α); HRMS (ESI) calculated for $C_{15}H_{32}FN_2O_5S$: 371.2010. Found 371.2022 (MH^+).

_N_-(dodecyl)-_N_'-(5-fluoro-α,β-D-arabinofuranosyl)sulfamide 2.38c



General Procedure B, using glycosyl sulfamide **2.37c** (50 mg, 0.1 mmol) and purification by flash chromatography (petrol: EtOAc, 1:1, R_f 0.1), afforded _N_-(dodecyl)-_N_'-(5-fluoro-α,β-D-arabinofuranosyl)sulfamide **2.38c** (32 mg, 78 %, α:β, 1:1) as a white solid; m.p. 129-131 °C (MeOH/DCM); υ_{max} (neat) 3293 (N-H), 1326 (s, S=O), 1142 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3CN) α anomer: 0.90 (3H, t, _J_ 6.8 Hz, C<u>H</u>$_3$), 1.26-1.38 (18H, m, 9 x C<u>H</u>$_2$), 1.48-1.57 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.91-3.04 (2H, m, C<u>H</u>$_2$NH), 3.91 (1H, at, _J_ 4.7 Hz, H-3), 3.96 (1H, at, _J_ 4.3 Hz, H-2), 4.03-4.11 (1H, m, H-4), 4.38-4.48 (1H, m, H-5), 4.50-4.60 (1H, m, H-5'), 4.91 (1H, d, $J_{1,2}$ 3.9 Hz, H-1), 5.06 (1H, br s, N<u>H</u>); β anomer: 0.90 (3H, t, _J_ 6.8 Hz, C<u>H</u>$_3$), 1.26-1.38 (10H, m, 5 x C<u>H</u>$_2$), 1.48-1.57 (2H, m, NHCH$_2$C<u>H</u>$_2$), 2.91-3.04 (2H, m, C<u>H</u>$_2$NH), 3.80-3.89 (1H, m,

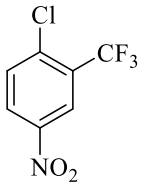
H-4), 3.91 (1H, at, *J* 4.3 Hz, H-3), 3.99-4.02 (1H, m, H-2), 4.38-4.48 (1H, m, H-5), 4.50-4.60 (1H, m, H-5'), 5.19 (1H, d, $J_{1,2}$ 4.3 Hz, H-1), 5.06 (1H, br s, N<u>H</u>); δ_C (100.5 MHz, CD_3CN) 13.4 (q, CH_3), 22.4, 26.5, 28.4, 29.0, 29.1, 29.3, 29.3, 29.4, 29.4, 31.6 (10 x t, 10 x CH_2), 43.0 (t, $NHCH_2\alpha$, $NHCH_2\beta$), 74.7, 75.5 (2 x d, $J_{C3\text{-}F}$ 6.9 Hz, C-3β, C-3α), 75.7 (d, C-2β), 80.0 (d, C-2α), 81.5 (d, $J_{C4\text{-}F}$ 19.1 Hz, C-4β), 81.6 (d, $J_{C4\text{-}F}$ 19.1 Hz, C-4α), 83.0 (d, $J_{C5\text{-}F}$ 168.6 Hz, C-5β), 83.3 (d, $J_{C5\text{-}F}$ 168.6 Hz, C-5α), 85.0 (d, C-1β), 89.1 (d, C-1α); δ_F (376.6 MHz, $CDCl_3$) -226.24 (td, $J_{F,H\ geminal}$ 49.6 Hz, $J_{F,H\ vicinal}$ 19.1 Hz, F-β), -228.44 (td, $J_{F,H\ geminal}$ 48.7 Hz, $J_{F,H\ vicinal}$ 22.9 Hz, F-α); HRMS (ESI) calculated for $C_{17}H_{36}FN_2O_5S$: 399.2323. Found 399.2331 (MH^+).

5.3 Experimental for chapter 3

General procedure A

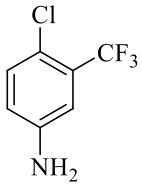
Amine **3.23** (1 equiv.) was dissolved in dry acetonitrile and the mixture stirred at 0 °C under nitrogen (5 mL). Triethylamine (3 equiv.) and sulfamoyl chloride (2 equiv.) were then added, the reaction was then allowed to warm to room temperature, and stirred for 2 h. Then the solvent was removed *in vacuo* to give a residue that was then purified by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient 0-45 % B; column oven: 40 °C; detection: UV 210nm and 280 nm) to afford sulfamide.

2-Chloro-5-nitrobenzotrifluoride 3.30[114]



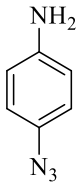
Conc. HNO_3 (2.7 mL, 0.06 mol) was added dropwise to conc. H_2SO_4 (3.1 mL, 0.06 mol). The resulting mixture was cooled to 20 °C and then 2-chlorobenzotrifluoride **3.29** (1 g, 5.5 mmol) was added. The reaction was stirred for 1 h at 50 °C until gas evolution ceased. After this time, t.l.c. (Petrol) indicated the formation of a single product (R_f 0.1). Iced water (50 mL) was then added carefully. The solvent was then removed *in vacuo* to give a residue that was then purified by flash chromatography to afford nitro compound **3.30** (0.9 g, 72 %) as pale yellow oil. δ_H (400 MHz, $CDCl_3$) 7.72 (1H, d, *J* 9.0 Hz, Ar-H-3), 8.35 (1H, dd, *J* 8.6, 2.7 Hz, Ar-H-4), 8.58 (1H, d, *J* 2.4 Hz, Ar-H-6).

5-Amino-2-chlorobenzotrifluoride 3.28a[114]



10 % Activated Pd-C (118 mg) was added to a solution of nitro compound **3.30** (1 g, 4.5 mmol) in methanol (20 mL). The flask was evacuated and purged with nitrogen five times, before being placed under an atmosphere of hydrogen. The solution was stirred for 2 h at room temperature. After this time, t.l.c. (petrol: EtOAc 4:1) indicated the formation of a product (R_f 0.5), and complete consumption of starting material (R_f 0.8). The reaction mixture was filtered through Celite® (eluting with methanol, 20 mL), and concentrated *in vacuo* to give a residue which was purified by flash column chromatography to afford aniline **3.28a** (1.2 g, 68.9 %) as yellow oil. δ_H (400 MHz, $CDCl_3$) 6.72 (1H, dd, *J* 8.4 Hz, 2.5 Hz, Ar-H-6), 6.95 (1H, d, *J* 2.7 Hz, Ar-H-5), 7.22 (1H, d, *J* 8.6 Hz, Ar-H-3).

4-Azidoaniline 3.28d[115]



Sodium ascorbate (345 mg, 1.7 mmol, 0.3 equiv.), CuI (330 mg, 1.7 mmol, 0.3 equiv.), L-proline (200 mg, 1.7 mmol, 0.3 equiv.) and NaOH (70 mg, 1.7 mmol, 0.3 equiv.) were added to a solution of 4-bromoaniline **3.31** (1g, 5.8 mmol, 1 equiv.) in

EtOH: H_2O (7:3, 30 mL). The resulting mixture was stirred for 15 minutes at room temperature. Then sodium azide (755mg, 11.6 mmol, 2 equiv.) was added and the reaction mixture was stirred at reflux for 3 h. After this time, t.l.c (DCM 100 %) indicated the formation of a single product (R_f 0.35), and complete consumption of starting material (R_f 0.4). The reaction mixture was cooled and concentrated *in vacuo.* The residue was dissolved in EtOAc (50 mL) and washed with water (3 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*, which was then purified by flash chromatography (DCM 100 %) to afford aniline **3.28d** (373 mg, 48 %) as brown solid. m.p 62-63 °C (DCM) [lit 65-66 °C][115,140]; δ_H (400 MHz, CD_3OD)[140] 6.60 (2H, d, *J* 8.6 Hz, Ar-H), 7.15 (2H, d, *J* 8.6 Hz, Ar-H).

General procedure for the synthesis of sulfamoyl chlorides 3.27a-d

Triethylamine (9 equiv.) was added to a solution of aniline **3.28a-d** (1 equiv.) in $CHCl_3$ (20 mL). Chlorosulfonic acid (1 equiv.) was added dropwise at -9 °C (ice and salt water mixture). The solution was then stirred at -2 °C for 1 h before it was concentrated *in vacuo.* The crude residue was dissolved in NaOH (1N, 20 mL) and then the resulting mixture was concentrated *in vacuo.* The residue was suspended in boiling ethanol. The insoluble solids were filtered off, and the filtrate was concentrated *in vacuo* to afford *N*-phenylsulfamate. The crude residue *N*-Phenylsulfamate was co-evaporated with toluene (3 x 30 mL) and then the residue was dissolved in toluene. PCl_5 (1 equiv.) was added and the reaction mixture was refluxed for 2 h, and then cooled to room temperature. The resulting suspension was

filtered, and the filtrate was concentrated *in vacuo* to afford sulfamoyl chloride **3.27a-3.27d**, which was used in the next step without further purification.

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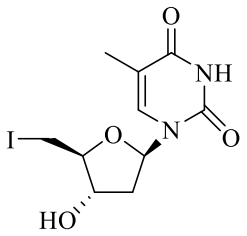
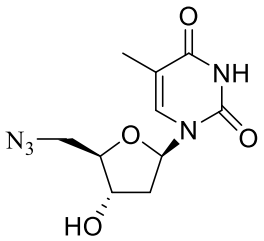
5'-Deoxy-5'-iodo-β-D-thymidine 3.25[141]



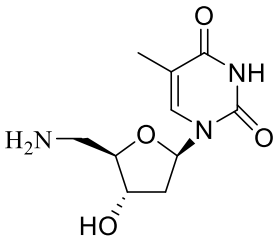
Thymidine **3.26** (1.0 g, 4.1 mmol, 1 equiv.) was dissolved in dry THF (25 mL) and triphenylphosphine (2.16 g, 8.2 mmol, 2 equiv.), iodine (1.57 g, 6.1 mmol 1.5 equiv.) and imidazole (421 mg, 6.1 mmol, 1.5 equiv.) were then added sequentially. The reaction mixture was then heated to 50 °C and stirred at for 16 h under nitrogen. After this time, t.l.c. (DCM : MeOH, 19:1) indicated the formation of a single product (R_f 0.2). The mixture was cooled, the solvent was removed *in vacuo*, and the residue was then dissolved in DCM (30 mL). The resulting solution was washed with 1 M aqueous HCl (20 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue that was then purified by flash chromatography (gradient elution, 100 % DCM to DCM: MeOH, 97:3) to afford iodide **3.25** (0.6 g, 41 %) as a white solid. m.p 168-170 °C (DCM/Petrol) [lit 170-173 °C][141]; $[\alpha]_D^{20}$ +22.8 (*c*, 1.0 in CH_3OH); δ_H (500 MHz, CD_3OD) 1.90 (3H, d, *J* 1.3 Hz, 5-CH_3), 2.26-2.34 (2H, m, H-2a', H-2b'), 3.43-3.53 (2H, m, H-5a', H-5b'), 3.83-3.86 (1H, m, H-4'), 4.29-4.32 (1H, m, H-3'), 6.28 (1H, t, $J_{1,2}$ 7.0 Hz, H-1'), 7.61 (1H, d, *J* 1.3 Hz, H-6).

5'-azido-5'-deoxy-β-D-thymidine 3.24[142]



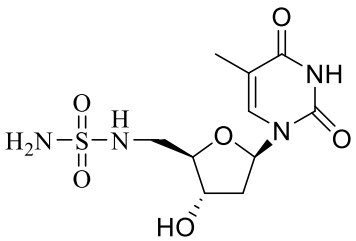
Iodide **3.25** (0.6 g, 1.7 mmol, 1 equiv.) was dissolved in dry DMF (10 mL), and NaN_3 (336 mg, 5.2 mmol, 3 equiv.) was then added. The reaction mixture was heated to 50 °C and stirred for 16 h under nitrogen. After this time, t.l.c. (EtOAc) indicated the formation of a single product (R_f 0.1), and the complete consumption of starting material (R_f 0.2). The mixture was cooled, the solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate (30 mL). The solution was washed with water (3 × 20 mL) and brine (20 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a residue that was then purified by flash chromatography (EtOAc 100%) to afford 5'-azido-2',5'-dideoxy-β-D-thymidine **3.24** (0.27 g, 70 %) as a white solid. m.p 157-159 °C (EtOH/Et_2O) [lit 161-163 °C][143]; $[\alpha]_D^{20}$ +66.4 (*c*, 0.5 in CH_3OH) [lit. $[\alpha]_D^{22}$ +89.5 (*c*, 0.94 in CH_3OH)][144] ; δ_H (500 MHz, CD_3OD) 1.89 (3H, d, *J* 1.1 Hz, 5-CH_3), 2.24-2.31 (2H, m, H-2a', H-2b'), 3.50-3.64 (2H, m, H-5a', H-5b'), 3.96 (1H, aq, *J* 3.9 Hz, H-4'), 4.33-4.37 (1H, m, H-3'), 6.26 (1H, t, $J_{1,2}$ 6.8 Hz, H-1'), 7.54 (1H, d, *J* 1.3 Hz, H-6).

5'-amino-5'-deoxy-β-D-thymidine 3.23[142]



Azide **3.24** (130 mg, 0.5 mmol, 1 equiv.) was dissolved in dry THF (10 mL). Triphenylphosphine (255 mg, 1.0 mmol, 2 equiv.) and water (0.02 mL, 1.0 mmol, 2 equiv.) were then added. The reaction mixture was stirred at room temperature for 16 h under nitrogen. After this time, t.l.c. (DCM: MeOH, 19:1) indicated the formation of a single product (R_f 0.0), and the complete consumption of starting material (R_f 0.6). The solvent was removed *in vacuo* to give a residue that was then purified by flash chromatography (2 % to 10% MeOH/DCM) to afford amine **3.23** (70 mg, 60 %) as a white solid. m.p 165-167 °C (EtOH/Et_2O); $[\alpha]_D^{20}$ +11.6 (*c*, 0.5 in CH_3OH); δ_H (400 MHz, CD_3OD) 1.75 (3H, s, 5-CH_3), 2.16-2.34 (2H, m, H-2a', H-2b'), 2.74-2.93 (2H, m, H-5a', H-5b'), 3.80-3.86 (1H, m, H-4'), 4.22-4.29 (1H, m, H-3'), 6.12 (1H, t, $J_{1,2}$ 6.8 Hz, H-1'), 7.30 (1H, s, H-6).

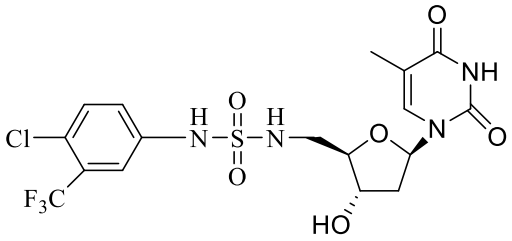
5'-Deoxy-5'-[*N*-(sulfamoyl)amino]-β-D-thymidine 3.10



General Procedure A, using sulfamoyl chloride, and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient:

the sample was run at 1 mL/min with a gradient of 0-45 % B; column oven: 40 °C; detection: UV 210 nm and 280nm), afforded sulfamide **3.10** (68 mg, 74 %) as a pale yellow waxy solid. $[\alpha]_D^{20}$ +14.3 (*c*, 0.35 in CH_3OH); υ_{max} (neat) 3268 (N-H), 1350 (s, S=O), 1170 (s, S=O) cm^{-1}; δ_H (400 MHz, D_2O) 1.76 (3H, s, 5-CH_3), 2.55-2.75 (2H, m, H-2a', H-2b'), 3.17-3.40 (2H, m, H-5a' and H-5b'), 4.28-4.36 (1H, m, H-4'), 5.03-5.12 (1H, m, H-3'), 6.01 (1H, t, $J_{1,2}$ 7.0 Hz, H-1'), 7.34 (1H, s, H-6); δ_C (100 MHz, D_2O) 11.3 (q, 5-CH_3), 35.2 (t, C-2'), 40.6 (t, C-5'), 79.7 (d, C-3'), 79.8 (d, C-4'), 88.0 (d, C-1'), 111.2 (s, C-5), 139.4 (d, C-6), 151.4 (s, C-2), 166.5 (s, C-4); HRMS (ESI) calculated for $C_{10}H_{17}N_4O_6S$: 321.0863. Found 321.0873 (MH^+).

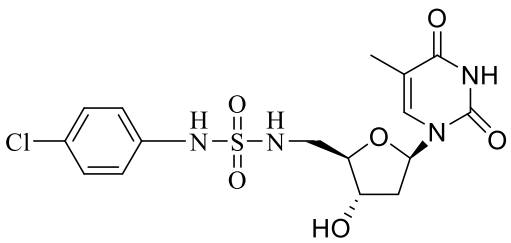
5'-Deoxy-5'-*N*-[*N*-(3-trifluoromethyl-4-chlorophenyl)sulfamoyl]amino]-β-D-thymidine 3.11



General Procedure A, using sulfamoyl chloride **3.27a,** and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 0-45 % B; column oven: 40 °C; detection: UV 210 nm and 280nm), afforded sulfamide **3.11** (43 mg, 65 %) as a pale yellow solid. m.p 105-107 °C (EtOH/Et_2O); $[\alpha]_D^{20}$ +10.3 (*c*, 0.35 in CH_3OH); υ_{max} (neat) 3273 (N-H), 1370 (s, S=O), 1165 (s, S=O) cm^{-1}; δ_H (500 MHz, CD_3OD) 1.86 (3H, d, *J* 1.0 Hz, 5-CH_3), 2.18 - 2.23 (2H, m, H-2a', H-2b'), 3.19 (1H, dd, $J_{5a',5b'}$

14.6 Hz, $J_{4,5a'}$6.6 Hz, H-5a'), 3.28 (1H, dd, $J_{5a',5b'}$ 13.6 Hz, $J_{4,5b'}$ 4.5 Hz, H-5b'), 3.85 - 3.87 (1 H, m, H-4'), 4.25 - 4.27 (1 H, m, H-3'), 6.11 (1H, t, $J_{1,2}$ 6.8 Hz, H-1'), 7.41 (1H, dd, *J* 8.9 Hz, 2.7 Hz, Ar-H-6), 7.47 (1H, d, *J* 1.0 Hz, H-6), 7.49 (1H, d, *J* 8.9 Hz, Ar-H-5), 7.57 (1H, d, *J* 2.7 Hz, Ar-H-2); δ_C (100 MHz, CD_3OD) 10.9 (q, 5-CH_3), 38.7 (t, C-2'), 44.2 (t, C-5'), 71.2 (d, C-3'), 84.6 (d, C-4'), 85.5 (d, C-1'), 110.3 (s, C-5), 117.3, 122.7, 131.9 (d, q, Ar(C)H, CF_3), 136.9 (d, C-6), 137.0, 138.0 (2 x s, 3 x Ar(C)), 150.8 (s, C-2), 164.9 (s, C-4); HRMS (ESI) calculated for $C_{17}H_{19}ClF_3N_4O_6S$: 499.0660. Found 499.0677 (MH^+).

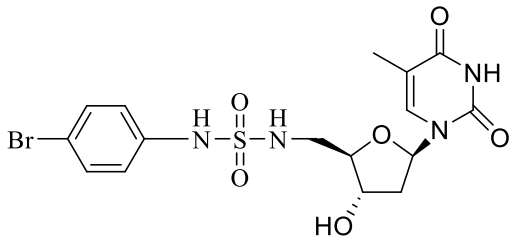
5'-Deoxy-5'-*N*-[*N*-(4-chlorophenyl)sulfamoyl]amino]-β-D-thymidine 3.12



General Procedure A, using sulfamoyl chloride **3.27b,** and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 0-45 % B; column oven: 40 °C; detection: UV 210 nm and 280nm), afforded sulfamide **3.12** (26 mg, 49 %) as a white solid. m.p 105-107 °C (EtOH/Et_2O); $[\alpha]_D^{20}$ +22.4 (*c*, 0.25 in CH_3OH); υ_{max} (neat) 3207 (N-H), 1328 (s, S=O), 1150 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3OD) 1.87 (3H, s, 5-CH_3), 2.20 (2H, at, *J* 6.3 Hz, H-2a', H-2b'), 3.13 - 3.28 (2H, m, H-5a' and H-5b'), 3.85(1 H, aq, *J* 4.7 Hz, H-4'), 4.28 (1 H, aq, *J* 5.1 Hz, H-3'), 6.12 (1H, t, $J_{1,2}$ 7.0 Hz, H-1'), 7.18, 7.26(4H, 2 x d, *J* 8.2 Hz, 4 x Ar-H), 7.50 (1H, s, H-6); δ_C (100

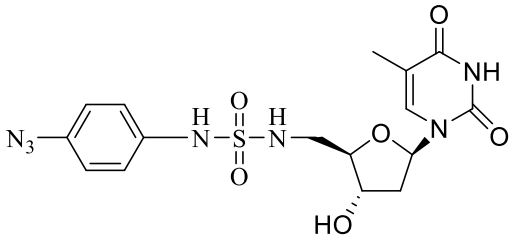
MHz, CD_3OD) 10.9 (q, 5-CH_3), 38.8 (t, C-2'), 44.2 (t, C-5'), 71.2 (d, C-3'), 84.7 (d, C-4'), 85.5 (d, C-1'), 110.3 (s, C-5), 120.3, 128.6 (2 x d, 4 x Ar(C)H), 137.0 (d, C-6), 137.2 (s, 2 x Ar(C)), 150.8 (s, C-2), 165.0 (s, C-4); HRMS (ESI) calculated for $C_{16}H_{20}ClN_4O_6S$: 431.0787. Found 431.0788 (MH^+).

5'-Deoxy-5'-*N*-[*N*-(4-bromophenyl)sulfamoyl]amino]-β-D-thymidine 3.13



General Procedure A, using sulfamoyl chloride **3.27c,** and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 0-45 % B; column oven: 40 °C; detection: UV 210 nm and 280nm), afforded sulfamide **3.13** (24 mg, 41 %) as a white solid. m.p 115-117 °C ($EtOH/Et_2O$); $[\alpha]_D^{20}$ +15.2 (*c*, 0.25 in CH_3OH); υ_{max} (neat) 3208 (N-H), 1386 (s, S=O), 1150 (s, S=O) cm^{-1} δ_H (400 MHz, CD_3OD) 1.87 (3H, s, 5-CH_3), 2.18 (2H, at, *J* 6.3 Hz, H-2a', H-2b'), 3.14 - 3.28 (2H, m, H-5a' and H-5b'), 3.85 (1 H, aq, *J* 5.1 Hz, H-4'), 4.27 (1 H, aq, *J* 4.7 Hz, H-3'), 6.11 (1H, t, $J_{1,2}$ 7.0 Hz, H-1'), 7.13 (2H, d, *J* 8.6 Hz, 2 x Ar-H), 7.40 (2H, d, *J* 9.0 Hz, 2 x Ar-H), 7.50 (1H, s, H-6); δ_C (100 MHz, CD_3OD) 11.0 (q, 5-CH_3), 38.8 (t, C-2'), 44.2 (t, C-5'), 71.2 (d, C-3'), 84.7 (d, C-4'), 85.5 (d, C-1'), 110.3 (s, C-5), 120.5, 131.7 (2 x d, 4 x Ar(C)H), 137.0 (d, C-6), 137.7 (s, 2 x Ar(C)), 150.8 (s, C-2), 165.0 (s, C-4); HRMS (ESI) calculated for $C_{16}H_{20}{}^{79}BrN_4O_6S$: 431.0281. Found 475.0281 (MH^+).

5'-Deoxy-5'-*N*-[*N*-(4-azidophenyl)sulfamoyl]amino]-β-D-thymidine 3.14



General Procedure A, using sulfamoyl chloride **3.27d,** and purification by RP-HPLC (Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 0-45 % B; column oven: 40 °C; detection: UV 210 nm and 280nm), afforded sulfamide **3.14** (18 mg, 34 %) as a light brown solid. m.p 133-135 °C ($EtOH/Et_2O$); $[\alpha]_D^{20}$ +10.4 (*c*, 0.25 in CH_3OH); υ_{max} (neat) 3219 (N-H), 1331 (s, S=O), 1148 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3OD) 1.86 (3H, s, 5-CH_3), 2.19 (2H, at, *J* 6.3 Hz, H-2a', H-2b'), 3.13-3.28 (2H, m, H-5a' and H-5b'), 3.86 (1 H, aq, *J* 4.7 Hz, H-4'), 4.27 (1 H, aq, *J* 5.1 Hz, H-3'), 6.11 (1H, t, $J_{1,2}$ 7.0 Hz, H-1'), 6.98, 7.23 (4H, 2 x d, *J* 8.6 Hz, 4 x Ar-H), 7.49 (1H, s, H-6); δ_C (100 MHz, CD_3OD) 12.8 (q, 5-CH_3), 40.6 (t, C-2'), 45.9 (t, C-5'), 72.9 (d, C-3'), 86.5 (d, C-4'), 87.3 (d, C-1'), 112.1 (s, C-5), 117.3, 122.2 (2 x d, 4 x Ar(C)H), 138.7 (d, C-6), 139.5 (s, 2 x Ar(C)), 152.6 (s, C-2), 166.8 (s, C-4); HRMS (ESI) calculated for $C_{16}H_{20}N_7O_6S$: 438.1190. Found 438.1200 (MH^+).

5.4 AB assay Protocol

5.4.1 Preparation of Growth Medium

5.4.1.1 Lysogeny Broth (LB) and LB/Tween 80 (LB/T)

LB was prepared by adding 20 g/L LB base (Invitrogen) to dH_2O. The pH was adjusted to 7 by the addition of 1 M NaOH as required. The resulting medium was sterilized by autoclaving in a culture flask or in individual 20 mL McCartney bottles. It was then stored at 4 °C for up to one month.

To prevent clumping of mycobacteria, Tween 80 was added to the LB to make LB/T. Before inoculation, sterile filtered Tween 80 was added to give a final concentration of 0.05 %. In order to sterile filter Tween 80, it was dissolved in 10x in distilled water, heated in the microwave until it was lukewarm and then vortexed, before it was filtered through a 0.2 µm membrane filter under a laminar flow hood.

5.4.1.2 LB Agar

LB agar was prepared by adding 20 g/L LB base (Invitrogen) and 15 g/L bacteriological agar (Oxoid) to dH_2O. 500 mL aliquots were autoclaved in 1000 mL bottles, and stored at room temperature until needed. The medium was then poured into sterile Petri dishes under a laminar flow hood, and stored at 4°C for up to one month.

5.4.1.3 Glycerol Freezer Stocks

A 50 % glycerol solution was made with distilled water and glycerol, and autoclaved. 700 µL of an overnight culture (OD_{600} ~ 0.4-0.6) was mixed with 300 µL of a 50 % glycerol solution before being snap frozen in liquid nitrogen and stored at -80 °C.

5.4.2 Preparation of *M. smegmatis* stocks:

A sterile LB agar plate was used to streak the *M. smegmatis* ($mc^2$4517 strain), and it was then incubated at 37 °C until visible colonies appeared, typically after 2-3 days.

After 2-3 days, a single colony was taken with a sterile pipette tip and transferred to a 10 mL (LB/T) McCartney bottle as a starter culture. The culture was incubated at 37 °C for 2-3 days at 160 rpm and until an OD_{600} of 0.4-0.6 was reached.

The cells were harvested by centrifugation at 2,500g in 2 x 50 mL sterile tubes at room temperature for 15 minutes and the media was removed. The cell pellets were re-suspended in sterile PBS + 0.05% Tween 80 (~ 25 mL per tube) and the cells were harvested by centrifugation by 2,500g at room temperature for 15 minutes. The supernatant was discarded and the cell pellets were re-suspended in 4 mL PBS + 0.05% Tween 80 (per 50 mL cell pellet). The cell suspensions were combined, and aliquot of 100 µl per cryo-tube were snap frozen in liquid nitrogen. The cells were stored at -80 °C.

5.4.3 Determine CFU/mL of Freezer Stocks

A 100 µL cryo tube containing the bacteria was taken from the freezer and thawed. 900 µL of LB/T was added and mixed by inverting 10-15 times. 100, 1000, 10,000 fold serial dilutions were made from this 10 times diluted stock. 250 µL of each dilution was added to an LB agar plate and spread using a sterile spreader. After incubation at 37 °C overnight, the cfu were counted. The cfu was found to be 1.8 x 10^5 cfu/mL.

cfu = number of colonies on plate * dilution factor * (1 mL/0.25 mL)

5.4.4 Assay plates:

In a sterile 96 well plate, 200 µl of dH_2O was added to the peripheral wells to prevent evaporation of the test wells. Then, 100 µl of LB/T media was added to all the wells in the series in columns **4-10**; 90 µl of the media was added to column **2** and 190 µl was added to column **3**. 10 µl of the test compounds ethambutol (64 µg/mL) and isoniazid (64 µg/mL) were added to columns **2** and **3** and each compound was tested in triplicates (**Figure 5.2**). Using a multichannel auto pipette, 100 µl of diluted compound samples was taken from the column **3** and was added to the next well (column **4**) which contained 100 µl of LB/T media. The well was then mixed 10 times, 100 µl of mixed compound was transferred to the next well (column **5**). This step was then repeated four times progressing up to the column **9** and then 100 µl of the solution were discarded from the last well (column **9**). Therefore the compounds were serially diluted by a factor of two across the plate, producing compound concentrations of 64, 32, 16, 8, 4, 2, 1 and 0.5 µg/ mL. Approximately 4.5 x 10^6 cfu of *M.smegmatis* was added per well in a volume of 100 µl (apart from column **11**). Control wells contained bacteria only (column **10),** 200 µl of medium only (column **11**). The plate was incubated at 37 ^{0}C for 18 hours. Thereafter, 10 µl of Alamar blue was added to all wells except the outer wells and the plate was then incubated for another 5 hours. The wells was observed after 5 hours for a colour change from blue to pink and the MIC value was determined by visual observation and also monitored spectrophotomerically at 595nm.

		1	2	3	4	5	6	7	8	9	10	11	12
	A	Water	Water	Water	Water	Water	Water	Water	Water	Water	Water	Water	Water
	B	Water	32	16	8	4	2	1	0.5	0.25	no inhibitor with cells	no inhibitor no cells	Water
EB	C	Water									no inhibitor with cells	no inhibitor no cells	Water
	D	Water		x2 fold inhibitor dilutions across the plate							no inhibitor with cells	no inhibitor no cells	Water
	E	Water									no inhibitor with cells	no inhibitor no cells	Water
INH	F	Water									no inhibitor with cells	no inhibitor no cells	Water
	G	Water									no inhibitor with cells	no inhibitor no cells	Water
	H	Water	Water	Water	Water	Water	Water	Water	Water	Water	Water	Water	Water

Figure 5.2: 96 well plate layout for in an AB assay with the drugs EMB and INH.

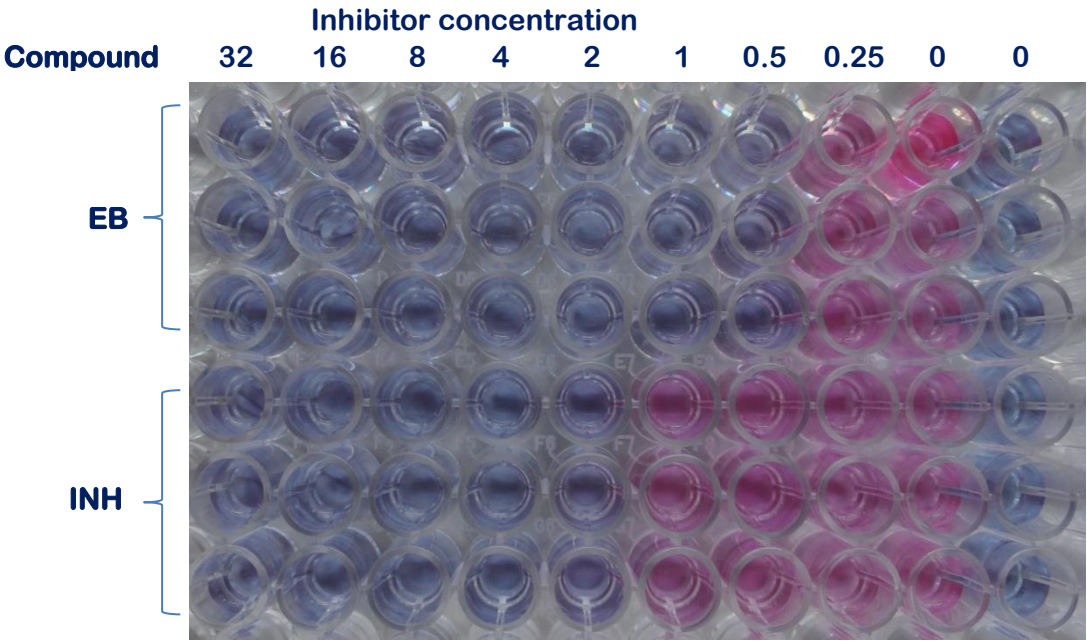


Figure 5.3: Alamar Blue assay plate for EMB and INH against *M. smegmatis*.

5.4 Experimental for chapter 4

General Procedure A: Reduction of polar azides

Azide (1 equiv.) was dissolved in MeOH (1 mL), and the resulting solution was added to a stirred solution of NaI (4 equiv.) and Amberlite IR 120 (1.8 meq/mL by wetted bed volume of exchangeable H^+ ions, 2 equiv.) in MeOH (1 mL). The reaction mixture was then concentrated on a rotary evaporator at 40 °C and 200 mbar until dryness (approx. 15 min.). The residue was dissolved in MeOH (5 mL), aqueous 1M HCl in MeOH (5 mL) and excess of Amberlite IR 120 (H^+ form) were then added. The Amberlite was eluted with MeOH (100 mL), then with H_2O (500 mL), and finally eluted with 2.5 M ammonia solution in MeOH.

General Procedure B: Reduction of non-polar azides

Azide (1 equiv.) was dissolved in $CHCl_3$ (1.5 mL), and the resulting solution was added to a stirred solution of NaI (4 equiv.) and Amberlite IR 120 (1.8 meq/mL by wetted bed volume of exchangeable H^+ ions, 2 equiv.) in MeOH (1 mL). The reaction mixture was then concentrated on a rotary evaporator at 40 °C and 200 mbar until dryness (approx. 15 min.). The residue was dissolved in MeOH (5 mL), aqueous 1M HCl in MeOH (5 mL) and excess of Amberlite IR 120 (H^+ form) were then added. The Amberlite was eluted with MeOH (100 mL), then with H_2O (500 mL), and finally eluted with 2.5 M ammonia solution in MeOH.

General Procedure C

Methanesulfonyl chloride (1.5 equiv.) was added dropwise to a stirred solution of the alcohol (1 equiv.) and Et_3N (1.5 equiv.) in anhydrous DCM (30 mL) at 0 ˚C under nitrogen. The reaction mixture was then allowed to warm to room temperature, and stirred for 2 hours. The reaction mixture was then poured into water (10 mL), and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in DMF (25 mL), sodium azide (3 equiv.) was added, and the mixture was stirred at 60 ˚C for 16 hours. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with distilled water (2 x 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and the residue was purified by column chromatography.

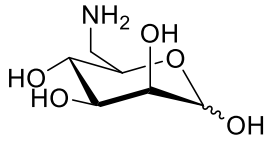
General Procedure D

Sodium azide (3 equiv.) was added to a solution of the halide (1 equiv.) in DMF (10 mL). The solution was then stirred at 50 ˚C for 16 hours. The reaction mixture was cooled, and diluted with diethyl ether (50 mL). The organic layer was separated and washed with water (2 x 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and the residue was purified by column chromatography.

General Procedure E

Glycoside (1 equiv.) was dissolved in dry THF (25 mL) and triphenylphosphine (2 equiv.), iodine (1.5 equiv.) and imidazole (1.5 equiv.) were then added sequentially. The reaction mixture was then heated to 50 °C, and stirred at for 16 h under nitrogen. The reaction mixture was then cooled to room temperature and the solvent was removed *in vacuo*. The residue was then dissolved in ethyl acetate (30 mL), and the resulting solution was washed with 10% w/v aqueous $Na_2S_2O_3$ (20 mL), and water (2 x 20 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo,* to give a residue that was purified by column chromatography.

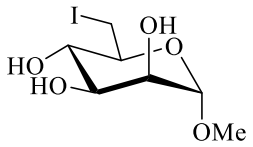
6-Amino-6-deoxy-D-mannopyranose 4.1



D-Mannose (0.5 g, 2.7 mmol, 1 equiv.) was dissolved in dry DMF (5 mL) and triphenylphosphine (1.45 g, 5.5 mmol, 2 equiv.), iodine (1.05 g, 4.2 mmol 1.5 equiv.) and imidazole (280 mg, 4.1 mmol, 1.5 equiv.) were added sequentially. The reaction mixture was then stirred at 50 °C for 3 h under nitrogen. After this time, t.l.c. (EtOAc: MeOH: H_2O, 7: 2: 1) indicated the formation of a single product (R_f 0.6). The solvent was removed *in vacuo* and the residue was dissolved in H_2O (30 mL). This solution was then washed with DCM (3 x 20 mL). The aqueous extracts were concentrated *in vacuo* to afford crude 6-deoxy-6-iodo-D-mannopyranose, as a yellow oil. This crude material was dissolved in DMF (25 mL), sodium azide (3 equiv.) was added, and the

mixture was stirred at 60 ˚C for 16 h. After this time, t.l.c. (EtOAc: MeOH: H_2O, 7: 2: 1) indicated the formation of a single product (R_f 0.5). The mixture was cooled, the solvent was removed *in vacuo*, and the residue was dissolved in H_2O (5 mL). This solution was then filtered through a column of Amberlite IR 120 (H^+ form), and then concentrated *in vacuo* to give a residue, which was purified by RP-HPLC [Luna C-18 column (Phenomenex); eluent: A (0.05 % TFA in H_2O) and B MeCN; gradient: the sample was run at 1 mL/min with a gradient of 0-100 % B; column oven: 40 °C; detection: CAD], to afford 6-amino-6-deoxy-D-mannopyranose **4.1** as pale yellow waxy solid (0.28 g, 56 %). υ_{max} (neat) 3330 (O-H); δ_H (400 MHz, D_2O) 2.97-3.12 (2H, m, H-6α, H-6β), 3.30 - 3.38 (2H, m, H-6'α, H-6'β), 3.42 - 3.58 (3H, m, H-4α, H-4β, H-3α/β), 3.73 (1H, dd, $J_{2,3}$ 2.3 Hz, $J_{3,4}$ 9.4 Hz, H-3α/β), 3.81 - 3.92 (4H, m, H-2α, H-2β, H-5α, H-5β), 4.81 (1H, s, H-1β), 5.08 (1H, s, H-1α); δ_C (100 MHz, D_2O) 40.4, 40.5 (t, C-6α, C-6β), 68.1, 68.1 (d, C-5α, C-5β), 68.4 (d, C-3α/β or C-4α/β), 69.8 (d, C-3α/β), 70.5, 71.0 (d, C-2α, C-2β), 71.7 (d, C-3α/β or C-4α/β), 72.6 (d, C-4α/β), 93.7 (d, C-1β), 94.0 (d, C-1α). HRMS (ESI) calculated for $C_6H_{14}NO_5$ ($M+H^+$): 180.0866. Found 180.0857.

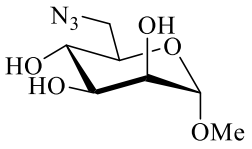
Methyl 6-deoxy-6-iodo-α-D-mannopyrannoside 4.4[145]



General procedure E, using methyl α-D-mannopyrannoside **4.3** (2 g, 10.3 mmol) and purification by flash chromatography (ethyl acetate: methanol: water, 7:2:1, R_f 0.5) afforded methyl 6-deoxy-6-iodo-α-D-mannopyrannoside **4.4** (2.3 g, 74 %) as a white

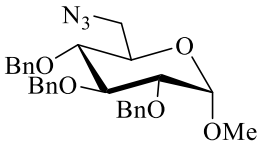
solid. m.p 120-123 °C (EtOH/Et_2O) [lit 118-120 °C][145]; $[\alpha]_D^{20}$ +76.2 (*c*, 0.5 in CH_3OH) [lit. $[\alpha]_D^{22}$ +67.5 (*c*, 1.0 in CH_3OH)][145]; δ_H (400 MHz, D_2O) 3.25 (1H, dd, $J_{6,6'}$ 10.6 Hz, $J_{5,6}$ 7.0 Hz, H-6), 3.32 (3H, s, OCH_3), 3.35-3.49 (1H, m, H-5), 3.45 (1H, t, $J_{3,4}$ 9.4 Hz, H-4), 3.52 (1H, t, $J_{6,6'}$ 11.0 Hz, H-6'), 3.64 (1H, dd, $J_{3,4}$ 9.4 Hz, $J_{2,3}$ 3.1 Hz, H-3), 3.80 - 3.83 (1H, m, H-2), 4.61 (1H, s, H-1).

Methyl 6-azido-6-deoxy-α-D-mannopyrannoside 4.5a[146]



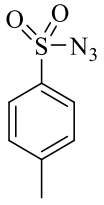
General procedure D, using methyl 6-deoxy-6-iodo-α-D-mannopyrannoside **4.4** (1 g, 3.3 mmol**)**, and purification by flash chromatography (ethyl acetate: methanol: water, 7:2:1, R_f 0.5) afforded methyl 6-azido-6-deoxy-α-D-mannopyrannoside **4.5a** (530 mg, 74 %) as a yellow oil. $[\alpha]_D^{20}$ +43 (*c*, 0.5 in CH_3OH) [lit. $[\alpha]_D^{24.3}$ +41 (*c*, 0.066 in CH_3OH)][146]; δ_H (400 MHz, CD_3CN) 3.37 (3H, s, OCH_3), 3.44 (1H, dd, $J_{5,6}$ 6.3 Hz, $J_{6,6'}$ 12.9 Hz, H-6), 3.48-3.62 (4H, m, H-3, H-4, H-5, H-6'), 3.76 (1H, dd, $J_{1,2}$ 1.6 Hz, $J_{2,3}$ 3.1 Hz, H-2), 4.64 (1H, s, H-1).

Methyl 6-azido-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 4.8a[147]



General procedure C, using methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **4.6** (1 g, 2.2 mmol), and purification by flash chromatography (petrol: ethyl acetate, 2:1, R_f 0.7) afforded methyl 6-azido-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **4.8a** (1 g, 95 %) as a pale yellow oil. $[\alpha]_D^{20}$ +51.3 (*c*, 1.0 in $CHCl_3$) [lit. $[\alpha]_D^{20}$ +53.1 (*c*, 2.4 in $CHCl_3$)][147]; δ_H (400 MHz, $CDCl_3$) 3.33 (1H, dd, $J_{6,6'}$ 12.9 Hz, $J_{5,6}$ 5.5 Hz, H-6), 3.40 (3H, s, OCH_3), 3.42 - 3.46 (2H, m, H-6', H-4), 3.54 (1H, dd, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.4 Hz, H-2), 3.78 (1H, td, $J_{4,5}$ 9.8 Hz, $J_{5,6}$ 5.9 Hz, $J_{5,6'}$ 2.3 Hz, H-5), 3.98 (1H, t, $J_{2,3}$ 9.2 Hz, H-3), 4.57 (1H, d, *J* 11.0 Hz, CH_2Ph), 4.61 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.67 (1H, d, *J* 12.1 Hz, CH_2Ph), 4.77-4.84 (2H, m, CH_2Ph), 4.90 (1H, d, *J* 11.0 Hz, CH_2Ph), 5.0 (1H, d, *J* 11.0 Hz, CH_2Ph), 7.23 - 7.40 (15H, m, Ar-H).

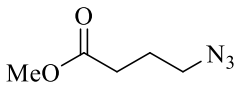
Toluenesulfonylazide 4.13a[148]



Sodium azide (511 mg, 7.9 mmol, 1.5 equiv.) was added to a solution of the toluenesulfonylchloride **4.9** (1 g, 5.2 mmol, 1 equiv.) in DMF (5 mL). The solution was then stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate (20 mL), and then the organic layer was separated and washed with water (2 x 30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered,

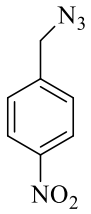
concentrated *in vacuo*, and the residue was purified by column chromatography (Petrol 100 %, R_f 0.1) afforded toluenesulfonylazide **4.13a** (0.7 g, 68 %) as a clear oil. δ_H (400 MHz, $CDCl_3$) 2.48 (3H, s, CH_3), 7.41, 7.84 (4H, 2 x d, *J* 8.2 Hz, 4 x Ar(C)H).

Methyl 4-azidobutyrate 4.14a[149]



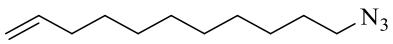
General procedure D, using methyl 4-chlorobutyrate **4.10** (1 g, 1.1 mmol), and purification by flash chromatography (petrol 100 %, R_f 0.4) afforded methyl 4-azidobutyrate **4.14a** (0.73 g, 70 %) as a clear oil. δ_H (400 MHz, $CDCl_3$) 1.87-1.95 (2H, m, CH_2), 2.41 (2H, t, *J* 7.4 Hz, $COCH_2$), 3.35 (2H, t, *J* 6.3 Hz, NCH_2), 3.69 (3H, s, OCH_3).

1-Azidomethyl-4-nitrobenzene 4.15a[150]



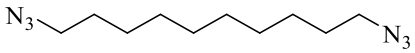
General procedure D, using 1-chloromethyl-4-nitrobenzene **4.11** (1 g, 5.8 mmol), and purification by flash chromatography (petrol: ethyl acetate, 5:1, R_f 0.4) afforded 1-azidomethyl-4-nitrobenzene **4.15a** (0.7 g, 67 %) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) 4.50 (2H, s, $PhCH_2$), 7.50, 8.25 (4H, 2 x d, *J* 8.6 Hz, 4 x Ar(C)H).

11-Azidoundecene 4.16a[151]



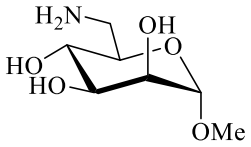
General procedure D, using 11-bromoundecene **4.12** (1 g, 4.3 mmol), and purification by flash chromatography (petrol: ethyl acetate, 2:1, R_f 0.9) afforded 11-azidoundecene **4.16a** (0.6 g, 71 %) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) 1.23-1.45 (12H, m, 6 x CH_2), 1.53-1.65 (2H, m, CH_2), 2.04 (2H, q, *J* 7.0 Hz, CH_2), 3.26 (2H, t, *J* 7.0 Hz, NCH_2), 4.90-5.03 (2H, m, $=CH_2$), 5.77-5.87 (1H, m, =CH).

1,10-Diazidodecane 4.18a[152]



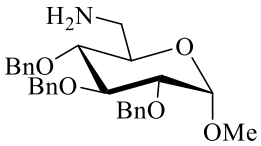
General procedure D, using 1,10-dibromodecane **4.17** (1 g, 3.4 mmol), and purification by flash chromatography (petrol 100 %, R_f 0.4) afforded 1,10-diazidodecane **4.18a** (0.6 g, 80 %) as a clear oil. δ_H (400 MHz, $CDCl_3$) 1.23-1.41 (12H, m, 6 x CH_2), 1.53-1.63 (4H, m, 2 x CH_2), 3.25 (4H, t, *J* 7.0 Hz, 2 x NCH_2).

Methyl 6-amino-6-deoxy-α-D-mannopyrannoside 4.5b[153]



General procedure A using methyl 6-azido-6-deoxy-α-D-mannopyrannoside **4.5a** (50 mg, 0.3 mmol), afforded methyl 6-amino-6-deoxy-α-D-mannopyrannoside **4.5b** (40 mg, 91 %) as a white foam. $[\alpha]_D^{20}$ +81 (*c*, 1.0 in CH_3OH) [lit. $[\alpha]_D^{23}$ +76 (*c*, 1.0 in CH_3OH)][153] ; υ_{max} (neat) 3340 (w, NH and OH) cm^{-1}; δ_H (400 MHz, CD_3OD) 2.96-3.03 (1H, m, H-6), 3.23 (1H, dd, $J_{6,6'}$ 13.1 Hz, $J_{5,6'}$ 2.9 Hz, H-6'), 3.39 (3H, s, OCH_3), 3.51 (1H, at, *J* 9.4 Hz, H-4), 3.56-3.62 (1H, m, H-5), 3.66 (1H, dd, $J_{3,4}$ 9.2 Hz, $J_{2,3}$ 3.3 Hz, H-3), 3.79 - 3.81 (1H, m, H-2), 4.66 (1H, d, $J_{1,2}$ 1.6 Hz, H-1); δ_C (100 MHz, CD_3OD) 41.2 (t, C-6), 54.2 (q, OCH_3), 68.4 (d, C-4), 70.1 (d, C-5), 70.5 (d, C-2), 70.7 (d, C-3), 101.6 (d, C-1); HRMS (ESI) calculated for $C_7H_{16}NO_5$ ($M+H^+$) 194.1023. Found 194.1023.

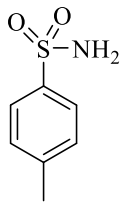
Methyl 6-amino-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 4.8b[154]



General procedure B, using methyl 6-azido-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **4.8a** (100 mg, 0.2 mmol), afforded methyl 6-amino-6-deoxy-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **4.8b** (88 mg, 93 %) as white solid. m.p 89-91 °C (Et_2O) [lit 86-89 °C][154]; $[\alpha]_D^{20}$ +41.2 (*c*, 0.25 in CH_3OH) [lit. $[\alpha]_D^{20}$ +54.8 (*c*, 1.0 in $CHCl_3$)][155]; υ_{max} (neat) 3392 (w, NH) cm^{-1}; δ_H (400 MHz, CD_3OD) 2.83 (1H, dd, $J_{6,6'}$ 13.1 Hz, $J_{5,6}$ 9.2 Hz, H-6), 3.15 (1H, dd, $J_{6,6'}$ 13.1 Hz, $J_{5,6'}$ 2.5 Hz, H-6'), 3.32-3.36

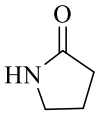
(1H, m, H-4), 3.41 (3H, s, OCH_3), 3.57 (1H, dd, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.4 Hz, H-2), 3.74 (1H, td, $J_{4,5}$ 9.4 Hz, $J_{5.6}$ 9.4 Hz, $J_{5,6'}$ 2.7 Hz, H-5), 3.89 (1H, at, *J* 9.2 Hz, H-3), 4.62 (1H, d, *J* 11.0 Hz, CH_2Ph), 4.70 (1H, d, *J* 11.0 Hz, CH_2Ph), 4.75 (2H, d, *J* 11.0 Hz, CH_2Ph), 4.77 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.87-4.95 (2H, m, CH_2Ph), 7.20 - 7.46 (15H, m, Ar-H); δ_C (100 MHz, CD_3OD) 40.9 (t, C-6), 54.7 (q, OCH_3), 67.8 (d, C-5), 72.7 (t, CH_2Ph), 74.5 (t, CH_2Ph), 75.1 (t, CH_2Ph), 78.8 (d, C-4), 79.9 (d, C-2), 81.2 (d, C-3), 97.8 (d, C-1), 127.3, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.4, 128.6, 128.7 (10 x d, 15 x Ar(C)H), 138.0, 138.1, 138.5 (3 x s, 3 x Ar(C)CH_2); HRMS (ESI) calculated for $C_{28}H_{34}NO_5$ ($M+H^+$) 464.2437. Found 464.2432.

Toluenesulfonamide 4.13b[156]



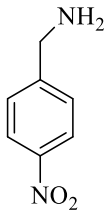
General procedure B, using toluenesulfonylazide **4.13a** (100 mg, 0.5 mmol), toluenesulfonamide **4.13b** (82 mg, 95 %) as a pale yellow solid; m.p 118-120 °C (Ethanol/Et_2O) [lit 125-126 °C][157]; υ_{max} (neat) 3258, 3355 (w, NH), 1385, 1154 (s, S=O) cm^{-1}; δ_H (400 MHz, CD_3OD) 2.41 (3H, s, CH_3), 7.34 (2H, d *J* 7.8 Hz, Ar(C)H), 7.77 (2H, d *J* 8.2 Hz, Ar(C)H) ; δ_C (100 MHz, CD_3OD) 20.0 (q, CH_3), 125.7, 129.1 (2 x d, 2 x Ar(C)H), 140.7, 142.7 (2 x s, Ar(C)SO_2, Ar(C)CH_3); HRMS (ESI) calculated for $C_7H_9NNaO_2S$ ($M+Na^+$) 194.0246. Found 194.0245.

2-Pyrrolidinone 4.14b[158]



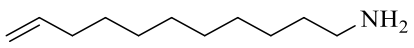
General procedure B, using methyl 4-azidobutyrate **4.14a** (100 mg, 0.7 mmol), afforded methyl 4-aminobutyrate **4.14b** (59 mg, quantitative yield) as a white waxy solid.; υ_{max} (neat) 1654 (s, C=O) cm^{-1}; δ_H (400 MHz, CD_3OD) 2.13-2.24 (2H, m, CH_2), 2.48 (2H, t, *J* 8.2 Hz, $COCH_2$), 3.50 (2H, t, *J* 7.0 Hz, NCH_2); δ_C (100 MHz, CD_3OD) 20.0 (t, CH_2), 29.8 (t, $COCH_2$), 43.3 (t, NCH_2), 180.9 (s, C=O); HRMS (ESI) calculated for C_4H_8NO ($M+H^+$) 86.0600. Found 86.0603.

(4-Nitrophenyl)methanamine 4.15b[159]



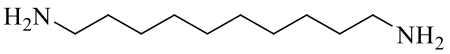
General procedure B, using 1-azidomethyl-4-nitrobenzene **4.15a** (100 mg, 0.6 mmol), afforded (4-nitrophenyl)methanamine **4.15b** (85 mg, quantitative yield) as a pale yellow waxy solid. υ_{max} (neat) 3308 (w, NH), 1541, 1350 (s, NO_2) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 4.16 (2H, s, $PhCH_2$), 7.74 (2H, d, *J* 8.6 Hz, 2 x Ar(C)H), 8.27 (2H, d, *J* 8.2 Hz, 2 x Ar(C)H); δ_C (100 MHz, DMSO-d_6) 42.0 (t, $PhCH_2$), 124.0, 130.5 (2 x d, 4 x Ar(C)H), 142.5, 147.8 (2 x s, 2 x Ar(C)CH_2); HRMS (ESI) calculated for $C_7H_9N_2O_2$ ($M+H^+$) 153.0659. Found 153.0659.

10-Undeceneamine 4.16b[160]



General procedure B, using 11-azidoundecene **4.16a** (100 mg, 0.5 mmol), afforded 10-undeceneamine **4.16b** (75 mg, 87 %) as a pale yellow waxy solid. υ_{max} (neat) 3426 (w, NH), 3119 (m, =CH), 1641 (m, C=C) cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.18-1.37 (12H, m, CH_2), 1.46-1.56 (2H, m, CH_2), 1.99 (2H, q, *J* 6.7 Hz, CH_2), 2.72 (2H, t, *J* 7.6 Hz, NCH_2), 4.88-5.01 (2H, m, $=CH_2$), 5.71-5.84 (1H, m, =CH); δ_C (100 MHz, DMSO-d_6) 26.3, 27.4, 28.7, 28.9, 29.2, 29.2, 33.6 (7 x t, 8 x CH_2), 39.2 (t, CH_2N), 115.1 (t, $=CH_2$), 139.3 (d, =CH); HRMS (ESI) calculated for $C_{11}H_{24}N$ ($M+H^+$) 170.1903. Found 170.1905.

1,10-Diaminodecane 4.18b[161]



General procedure B, using 1,10-diazidodecane **4.18a** (100 mg, 0.4 mmol) and 8. equiv. of NaI and 4 equiv. of acid, afforded 1,10-diaminodecane **4.18b** (70 mg, 92 %) as a white solid. m.p 66-68 °C ($MeOH/Et_2O$) [lit 62-64 °C][161]; υ_{max} (neat) 3420 (w, NH) cm^{-1}; δ_H (400 MHz, CD_3OD) 1.32-1.43 (12H, m, 6 x CH_2), 1.60-1.70 (4H, m, 2 x CH_2), 2.91 (4H, t, *J* 7.4 Hz, 2 x NCH_2); δ_C (100 MHz, CD_3OD) 26.0, 27.2, 28.8, 29.0 (4 x t, 8 x $\underline{C}H_2$), 39.4 (t, 2 x $N\underline{C}H_2$); HRMS (ESI) calculated for $C_{10}H_{25}N_2$ ($M+H^+$) 173.2012. Found 173.2010.

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